RADIOLOGY

A MONTHLY JOURNAL DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

Vol. 52 MARCH, 1949 No. 3

CONTENTS

On the Scientific Evaluation of Diagnostic Procedures: Presidential Address. *L. Henry Garland, M.D.* 309

Angiocardiography in Congenital Heart Disease of Cyanotic Type with Pulmonic Stenosis or Atresia. I. Observations on the Tetralogy of Fallot and "Pseudo-Truncus Arteriosus." *Robert N. Cooley, M.D., Henry T. Bahnson, M.D., and C. Rollins Hanlon, M.D.* 329

Aid of Arteriograms in Diagnosis and Treatment of Intracranial Aneurysms. *James L. Poppen, M.D.* 347

The Angiocardiographic Measurement of the Normal Great Vessels. *Charles T. Dotter, M.D., and Israel Steinberg, M.D.* 353

A Roentgen Finding of Unusual Interest in Perforation of the Colon. *Charles Gottlieb, M.D., Herbert S. Sharlin, M.D., and William Peck, M.D.* 359

The Linear Atelectatic Sign in Intra-Abdominal Lesions. *Jerome L. Marks, M.D., and Alvin Nathan, M.D.* 363

Dysgerminoma. Case with Pulmonary Metastases; Result of Treatment with Irradiation and Male Sex Hormone. *P. E. Russo, M.D., and J. W. Kelso, M.D.* 367

The Hematological Effects of Ionizing Radiations. *Leon O. Jacobson, M.D., Edna K. Marks, and Egon Lorenz, Ph.D.* 371

The Lethal Dose of Total-Body X-Ray Irradiation in Swine. *John L. Tullis, M.D., Carl F. Tessmer, M.D., Eugene P. Cronkite, M.D., and F. W. Chambers, Jr., B.S.* 396

Aberrant Tissue Developments of Rats Exposed to Beta Rays. The Late Effects of P^{32} Beta Rays. *P. S. Henshaw, Ph.D., R. S. Snider, Ph.D., and E. F. Riley* 401

Use of a Plastic Tracheal Cannula, with Report of a Case. *James C. Barnett, M.D., Ira A. Polisar, M.D., and Robert S. Polisar, D.D.S.* 416

A Rapid Cassette Changer for Angiocardiography. *Merrell A. Sisson, M.D.* 419

Photographic Effect of Various Radiations on Special Dental Packets. *Russell F. Cowing and Charles K. Spalding* 423

Editorial: The Action of Radiation on Living Cells. *Harold W. Jacox, M.D.* 428

Announcements and Book Reviews. 431

In Memoriam. 436

Radiological Societies: Secretaries and Meeting Dates. 440

Abstracts of Current Literature. 443

RADIOLOGY

A MONTHLY PUBLICATION DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

PUBLISHED BY THE RADIOLOGICAL SOCIETY OF NORTH AMERICA

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RADIOLOGY is entered as second class matter at Syracuse, New York, and Easton, Penna., under the Act of August 24, 1912, and accepted November 24, 1934. RADIOLOGY is published by the Radiological Society of North America as its official Journal. Subscription rate $8.00 per annum. Canadian postage, $1.00 additional. Foreign postage, $2.00 additional. Single copies $1.00 each. All correspondence relative to business matters connected with the Radiological Society of North America and RADIOLOGY, or remittance for non-member subscriptions, should be made payable to the Radiological Society of North America and should be addressed to the BUSINESS MANAGER, DONALD S. CHILDS, M.D., 713 E. GENESEE STREET, SYRACUSE 2, NEW YORK. In requesting change of address, both the old and the new address should be given.

Dues to the Radiological Society of North America include subscription to RADIOLOGY and should be paid to DONALD S. CHILDS, M.D., SECRETARY-TREASURER, 713 E. GENESEE STREET, SYRACUSE 2, N. Y.

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Vol. 52 MARCH 1949 No. 3

On the Scientific Evaluation of Diagnostic Procedures

Presidential Address

Thirty-fourth Annual Meeting of the Radiological Society of North America[1]

L. HENRY GARLAND, M.D.

San Francisco, Calif.

DIAGNOSIS IS the cornerstone of modern clinical medicine. It requires accurate observation and rational deduction. In its most complete form it is the process of identifying a disease by consideration of the history, symptoms, physical signs, and results of every other type of examination of the patient; it includes differential diagnosis and provides a basis for prognosis. It is realized, however, that often the process contains some element of uncertainty so that diagnosis might be defined as "the procedure of reaching the *most probable* conclusion based on the facts at hand."

This element of uncertainty extends to all branches of medicine. In those branches in which it has been measured—for example in pediatrics, clinical laboratory work, and chest surveys—it is found to be significant in degree, and therefore worthy of attention. As a result of this attention, methods for its correction or reduction can be evolved.

Roentgenologic examination of the chest is one of the most important diagnostic procedures developed in the last half century. The results of its use are highly reliable so long as they are integrated with the other clinical findings, the history, the symptoms, and the laboratory data. When the method is used as the sole examination, however, as occasionally happens in everyday practice, its reliability may be evanescent.

In recent years, roentgen examination of the chest as employed in mass radiography has been called upon by some to serve as a decisive diagnostic test. This has put an undue stress on the procedure. Further, instead of the medium usually employed in clinical practice, a small film process has been generally utilized.

In order to investigate the relative diagnostic efficiency of the various roentgenographic and photofluorographic technics used in mass-survey work, a Board of Roentgenology was appointed in 1944 (4). This Board was made up of three chest specialists and two radiologists, and had the services of a biostatistician. Each member made independent interpretations of four sets of films and found to his astonishment that not only did he differ from his colleagues in apparently simple interpretations, but that he even differed with him-

[1] Delivered in San Francisco, Dec. 6, 1948.

This address embodies a preliminary report on a research program of a committee of three radiologists (Earl Miller, M.D., Henry Zwerling, M.D., and the author), aided by Jacob Yerushalmy, Ph.D. To these three co-workers, I wish to express my deep appreciation. Their efforts and co-authorship are manifest throughout this report. To Professor Yerushalmy we are especially indebted for the statistical analyses.

self in a significant percentage of the same films which he read on two separate occasions. The Board recommended that this phenomenon be subjected to extensive and detailed investigation. This paper constitutes a summary of certain phases of the investigation thus far pursued, and of certain deductions arising from this work.

OBSERVATIONS IN OTHER FIELDS

In all human activities the "human equation" is present to a greater or lesser degree. In nearly every activity which can be tested, it has been repeatedly demonstrated that humans, even experts in a given field, exhibit enormous variations in their ability to be consistent with themselves and others equally competent (7, 10, 11). For example, Williams (10) reports an experiment in which the taste of a chemical was tested in a study of 6,377 persons. Of those who took it, 21 per cent found it tasteless, 65 per cent found it bitter (many extremely so), 2 per cent found it sweet, 5 per cent found it sour, 5 per cent found it salty, and the remaining 2 per cent ascribed to it other miscellaneous characteristics.

The medical profession, being composed of human beings, cannot be expected, despite long study and training, to be entirely free of this foible. Indeed *in such tests as have been made*, they have been shown to exhibit comparable variation both in clinical and in laboratory work. The following are a few examples, and are given, not to discredit the art, but to illustrate the problems found by some of those who have had the opportunity to investigate:

Evaluation of Clinical Judgment

(*a*) *Nutritional Studies:* A group of 5 experienced pediatricians (6) was asked to classify 221 children according to their nutritional status. They made complete clinical examinations and employed such diagnostic aids as they desired. In the entire series, the number of children reported by the different pediatricians as suffering from malnutrition varied from 32 to 47; moreover, these were *not* the same cases! There were 90 in which one or the other examiner diagnosed malnutrition. There were only 7 cases of malnutrition in which all five examiners agreed.

(*b*) *Tonsil Disease Studies:* The American Child Health Association conducted a study of 1,000 eleven-year-old school children (2). Of these, about 611 had had their tonsils removed. The remaining 389 were then examined by physicians, who selected 174 for tonsillectomy and rejected the rest. This left 215 children whose tonsils were apparently all right. Then, however, another group of doctors was put to work examining these 215 children. This time 99 of the youngsters were adjudged to be in need of tonsillectomy. So still another group of doctors was employed to examine the remaining children and nearly one-half of these were selected by the examiners for operation. In the end, only sixty-five of the original group of a thousand children remained whose tonsils had not been either removed or recommended for removal. Had these sixty-five been examined by a fresh lot of physicians the number might have been reduced still further, but at this stage the investigation was concluded.

"The study showed," says Dr. Harry Bakwin, "that there was no correlation whatsoever between the estimate of one physician and that of another regarding the advisability of tonsillectomy, and the authors therefore concluded that the chance of a child being recommended for operation depended principally on the physician rather than on the child's health status." He adds that analysis showed that economic considerations played no part in the recommendations.

(*c*) *Axillary Palpation Examinations:* It is well known that there is a large factor of error in the accuracy of the clinical diagnosis of axillary node metastasis. While we do not have data on the differences between physicians examining identical cases, we believe that the following published facts give a clue to the probable degree of variation present (8):

Author	Clinical Diagnosis of Involved Nodes, But No Cancer Found in Nodes at Operation	Clinical Diagnosis of No Palpable Nodes, But Cancerous Nodes Found at Operation
Harrington	32 per cent	29 per cent
Haagensen	15 per cent	44 per cent
Siris and Dobson	29 per cent	14 per cent

Evaluation of Laboratory Procedures

Clinical laboratory procedures are analogous to radiological studies in that single results are often accepted at face value and indeed are accorded decisive import in some cases. It is therefore instructive to review a recent critical analysis reported by Belk and Sunderman (3).

A number of carefully prepared solutions were distributed among 59 different hospital clinical laboratories for analysis. The results of this study showed enormous variation in the reports of the different laboratories (see Table I). For instance, one sample of hemoglobin was prepared to contain 9.8 gm. per 100 c.c. The reports from the laboratory gave a range of 8.0 to 15.5 gm. Fully 67 per cent of the reports were regarded as beyond the reasonable range of error; 22 per cent were regarded as showing gross error. Similar results may be noted for the other solutions.

The above observations give a clue as to the frequency and magnitude of error in various fields which have been measured. The serious student must conclude that it is highly probable that a similar degree of imperfection exists in many fields. This is no cause for despondency; on the contrary, its study is evidence of intellectual maturity, and will serve the invaluable purpose of leading toward improved diagnosis and methods of treatment.

While radiology shares with other medical procedures this element of aberration, it has the good fortune of doing so to no greater a degree than most, as will subsequently be shown. It is still, relatively speaking, an accurate and invaluable diagnostic aid, and fortunately it lends itself to exact evaluation.

INITIAL STUDIES

In 1944, a series of studies was made in order to test the diagnostic value of the different roentgen recording media used in mass surveys of the chest (4). The results were subjected to critical analysis and statistical study, and it was found that not one of the various film methods was superior for *case-finding* purposes to any of the other methods. In the process of analyzing the results, it was observed that there was a significant percentage of over- and under-reading. That is, films read by a majority of readers as negative (and apparently negative by all known criteria) were read as positive by some readers—*over-reading or false positives*. Conversely, some films accepted as positive by a majority, *i.e.*, as showing x-ray evidence of disease, were read as negative by other readers—*under-reading or misses*. Further, the same reader was inconsistent with himself in a surprising number of instances, on both scores, when the same films were read on two separate occasions.

These errors were initially attributed to technic, to the factor of small lesion, and

TABLE I: AN EVALUATION OF CLINICAL LABORATORY PROCEDURES SHOWING VARIATIONS IN THE RESULTS OF CHEMICAL ANALYSES OF STANDARD SOLUTIONS IN DIFFERENT LABORATORIES

Selected from Table I, Belk and Sunderman (3)

Substance Tested	Concentration, as Prepared, per 100 Ml.	Range of Actual Results	Percentage of Determinations Classified as Satisfactory, Unsatisfactory and Gross Error		
			Satisfactory	Unsatisfactory	Gross Error
Hemoglobin	9.8 gm.	8.0–15.5 gm.	33	67	22
Glucose	60.0 mg.	40–570 mg.	63	37	10
Sodium chloride	465.0 mg.	350–775 mg.	68	32	5
Total protein	6.6 gm.	4.7–12 gm.	38	62	15
Calcium	6.6 mg.	3–18 mg.	33	67	28

to the "human equation." They were measured by a study of the relative frequency with which a reader was inconsistent with other readers (*inter*-individual variation) and with himself on two separate readings of the same set of films (*intra*-individual variation).

The degree of *inter*-individual variation, based only on the positives and *not* on all cases read, was from 9 to 24 per cent. This variation included cases of extensive disease, and was *not* due to the fact that only small or difficult lesions were being analyzed. Variation can be measured in different ways. As an example, if in a set of 100 films there are 4 positive and 96 negative films and a reader selects only 2 of the positive, and calls the remaining 98 negative, he might be regarded, by one standard, as being only 2 per cent wrong or inconsistent. On the other hand, if the set of films consists of survey material, the object of which is to detect all the positives, he might be regarded as 50 per cent wrong. In the percentages recorded in these paragraphs, the second criterion is being used.

The degree of *intra*-individual or personal variation was from 3 to 31 per cent. This degree of variation was surprising to many, even to persons whose scientific training and background should have led them to anticipate it, in view of the known element of error in all fields.

THE C. R. N. RESEARCH PROGRAM[2]

Having discovered the relatively high and quite unexpected degree of variation in reading "routine chest films" above described, a committee of three expert radiologists was appointed by the Division of Tuberculosis Control of the U. S. Public Health Service to make a thorough investigation of the problem. These radiologists were authorities and teachers of international repute, and above cavil.

[2] C. R. N. represents the initials of three radiologists on the first panel; G. M. Z. the initials of the members of the second committee. Both groups worked with the assistance of Dr. J. Yerushalmy. It would be impossible in the space at our disposal to describe even in brief form the vast amount of work done by the C. R. N. group on this entire problem to date. This short preliminary summary of a few phases is being published with their kind permission.

Initially the committee read a prepared set of one hundred 14 × 17-inch celluloid films twice and, not without chagrin, reached results similar to those of the earlier study. (These 100 films have subsequently been read by seven other leading radiologists and chest specialists in the United States, with similar results. The enigma is therefore quite general, and not of circumscribed proportion.) It was the impression of the C. R. N. group that the problem had its main origin in terminology or semantics. Accordingly, the method of approach was that of devising new and mutually understandable terms.

This common understanding was essayed in group conferences and experimentation of considerable duration. Practically all known terms used by physicians in interpreting chest films were subjected to careful tests. It was assumed that a term had utility only to the extent that it meant the same thing to the same or different readers on different occasions. By this test, all conventional terms were found wanting. Take, for example, the terms "hard" and "soft." A shadow interpreted as "hard" by one reader was apt to be read as "soft" by another, or even by the same reader on a different occasion. Similarly for the terms "exudative" and "productive," etc.

This led the group to eliminate from their trials any attempt at prognostication and to concentrate on simple description of the lesions. After many sessions, efforts were made to use only three principal terms in describing a given lesion: the shadows were called "*honeycombed*," "*spotted*," or "*smooth matrix*" (*i.e.*, uniform). Since few lesions are entirely of one characteristic, the group devised a triangle on which to record their various findings.

Each corner of the triangle was marked with one of the terms. Lesions were recorded by marking a dot in the triangle as near as possible to the appropriate term, making allowance for the proportion of one or more of the three characteristic appearances which it possessed. It is of interest to review the results of this method on a set

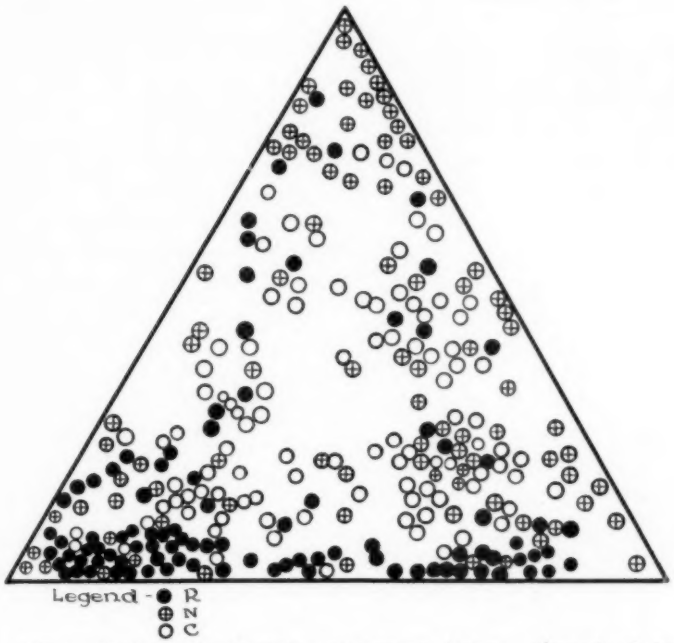

Fig. 1. Variations in description of roentgen shadows. Example of the C. R. N. triangle used in one of their several sets of *Descriptive Tests*.

The corners of the triangle refer to the following apparent characteristics of the roentgen shadow: Apex = "Smooth matrix" (uniform density); Left lower corner = "Spotted" shadow ("mottling"); Right lower corner = "Honeycombed" shadow.

Each predetermined zone in the roentgenogram is represented by three dots of different form, one for each reader. The illustration shows the variation in interpretations of the three observers and their individual "tendencies" to interpret or describe shadows in different terms. Reader R is apt to "see" a lesion as spotty, reader N as more uniform, etc. For details see text.

of 100 films. The combined readings of the 3 investigators are shown in Figure 1. It is evident that while there are specific tendencies for each of the readers, there is little conformity. Reader "R" is likely to record lesions as heterogeneous (toward the spotted side), while "N" sees the same as more uniform (smooth matrix), and "C" tends to avoid either extreme, recording lesions as being composed of all three characteristics. Nevertheless it was found that this method greatly reduced the *intra*-individual variation, though it left the *inter*-individual variation as large as before.

At this point, reached after some two years of study,[3] the C. R. N. group felt that more frequent personal contact between the investigators was desirable, and therefore sought the appointment of a second committee of experienced radiologists who could and would meet frequently. As a result, the G. M. Z. group was formed.

THE G. M. Z. STUDIES[4]

The G. M. Z. group attacked the problem which they inherited from the first committee with humility born of the experience of that distinguished panel. It was

[3] During this time, one of us (G) conducted a series of tests on younger radiologists to determine (*a*) their ability to read survey films and (*b*) their consistency. A set of fifty 14 × 17-inch films was read twice, several weeks apart, by 7 different readers. Based on all cases read, the *inter*-individual disagreement was from 14 per cent upwards. The *intra*-individual inconsistency was from 6 to 48 per cent. The latter was then retested on another group of 6 readers, mostly residents in training; the inconsistency remained of a high order. We started believing we could read films quite reliably and suspect activity from "soft" shadows and obsolescence from "hard" ones. We ended up just as humbled as the experts.

[4] Aided by a grant from the Division of Tuberculosis Control of the U. S. Public Health Service, F. S. A.

Reader_____ Date_____ Set of Films _____

Reading:____1st____2nd____3rd_____

Film No.	A Don't Follow	B Further Study	1 Neg.	2 Lung Lesion	3 Pleural Lesion	4 Other Process* (H.A.M.B.)	5 Remarks
					*Heart, Aorta, Mediastinum, Bone.		

Fig. 2. Check sheet used in first four sets of mass survey readings by G. M. Z., to test an interpreter's ability (*a*) to *see* a lesion, and (*b*) to *evaluate* its possible significance.

For example, a small, dense calcified focus might be read as "A 2," *i.e.*, lung lesion present, but no follow-up needed. An area of infiltration would be read as "B 3," etc. In these tests, only one entry was made for each film—the predominant pertinent infectious process, if any.

obvious from the results obtained by C. R. N. that the solutions to the fundamental problems involved in the phenomenon of film interpretation, especially those of description of a lesion, would be obtained only after long experimentation and study. It would require not only the talents of radiology but those of a number of associated disciplines in the medical, biological, and allied sciences, including philology and philosophy. The committee, therefore, thought it wiser to "make a fresh start" and pursue the problem in its own way rather than to retrace the steps followed by C. R. N. It attempted from the beginning to distinguish between the three main components of the problem, *i.e.*, (*a*) seeing a lesion; (*b*) describing a lesion; (*c*) evaluating a lesion.

The group decided first to attempt an evaluation of the problems involved in "seeing a lesion" before proceeding to the more difficult and fundamental ones of describing and evaluating it.

Seeing a Lesion

In broad terms the problems involved in studying the ability of an observer to detect an abnormal roentgen shadow may be divided as follows: (*a*) To determine re-

liable methods for measuring the relative number of lesions missed by a reader. This is essential not only as a base line for further work in the study of the phenomenon and to afford a measure of progress in its reduction, but also as a practical tool for evaluating and testing prospective readers in mass survey work. (*b*) To study the probable reasons for missing lesions and their characteristics. (*c*) To investigate methods of interpretation which might lead to a reduction in the number of lesions missed.

The group studied all these three phases, and, although it does not have final solutions, sufficient progress has been achieved to justify this preliminary report.

(*a*) *Method for Measuring Lesions Missed:* In its attempts to evaluate the magnitude of variation in seeing a lesion, the group believed that it is necessary to distinguish between three components: inconsistency, under-reading, and over-reading. For the last two components, it is essential to know which of the films is positive; for the first this is not necessary. If a set of 100 films were read independently twice by the same or two different readers, a number of films would be interpreted differently in the two attempts. This number represents a measure of the consistency or inconsistency of the readers without any relationship to the probable presence or absence of a lesion. However, consistency *per se*, although a necessary requirement, is not in itself sufficient. In order for a person to be a competent interpreter, he must be not only relatively consistent with himself, but he must be consistently *right*. In addition, therefore, to measures of consistency, it becomes important to obtain measures for *under-reading*, that is missing a positive[5] film (false negative), and for *over-reading*, that is calling a negative film, positive (false positive).

The answers obtained by G. M. Z. to these questions are based on the readings of three sets totaling 399 films, employing the form shown in Figure 2. The magnitude of *inconsistency* is shown in Table II. From the experience of G. M. Z. it is therefore possible to state that, if a set of similar films is read by two different observers, the likelihood is that in 16 per cent of the cases the two readers will disagree with each other as to whether or not a lesion is present. If the same person re-reads the same set of films, he is likely to disagree with himself in approximately 8 per cent of the cases.

TABLE II: EVALUATION OF CONSISTENCY IN "SEEING A LESION"

Number and Percentage of Disagreements between Readers (Inter-individual) and for Different Interpretations by the Same Reader (Intra-individual) on 399 Films Interpreted Twice by Each of Three Readers

	Inter-individual Comparison	Intra-individual Comparison
Number of films	399	399
Number of pairs of readings on each film	12	3
Total number of pairs of readings—all films	4788	1197
Number of pairs of readings essentially in agreement	4015	1101
Pairs of readings in complete disagreement	773 (16.2%)	96 (8.0%)

Two comments must be made to assist the reader in evaluating these percentages. First, the magnitude of inconsistency is obviously a function of the material included in the test series. (Although efforts were made to select the test films with great care,[6] it is obvious that a different selection containing other proportions of positives and negatives and films of other degrees of difficulty might produce different results. It must be stated, however, that no significantly different results were obtained by G. M. Z. on the three different sets of films which they have read to date.) The second comment refers to the definition employed in calling two readings inconsistent. For the percentages quoted,

[5] In order to avoid cumbersome terminology, the words "positive" and "negative" are used to indicate whether, in the opinion of the reader, the film contained *x-ray evidence of disease* or not.

[6] Selected without the knowledge of the readers by a competent radiologist in consultation with the statistical advisor.

TABLE III: EVALUATION OF UNDER-READING AND OVER-READING IN FILM INTERPRETATION

Number and Percentage of Under-Reading (False Negatives) on Films Assumed to Be "Positive" on the Basis of a Majority Opinion, and Number and Percentage of Over-Reading (False Positives) on Films Assumed to Be "Negative" on the Basis of a Majority Opinion, Based on 399 Films Interpreted Twice by Each of Three Readers

	Films Considered "Positive" (4 or More "Positive" Readings Out of 6)	Films Considered "In-Between" (3 "Positives" Out of 6)	Films Considered "Negative" (2 or Less "Positives" Out of 6)
Number of films	162	26	201
Expected* number of readings			
"Positives"	972	156?	0
"Negatives"	0	0?	1206
Number of readings recorded			
"Positives"	905	78	145
"Negatives"	67	78	1044
Percentage of under-reading	6.9	50.0	...
Percentage of over-reading	...	50.0	12.2†

* That is, 2 readings by each of 3 readers, or 6 readings: 6 × 162 = 972 maximum possible "positives" and so on.

† This figure is inexplicably high. It may be a reflection of the material sampled plus the conditions under which the tests were conducted.

two readings were considered in disagreement if they were totally contradictory. One reading had to be recorded as B 2, 3, or 4, that is "The case requires follow-up and there is a lesion either in the lung, pleura, or in the bony structures," while the other reading had to be A 1, that is "The case does not require follow-up and there is no lesion anywhere." Two readings such, for example, as "There is a lesion requiring follow-up" and "There is a lesion, but no follow-up seems indicated" were not considered in this comparison as constituting disagreement.

In the percentages presented above, no account was taken as to which of the readings is likely to be the correct one. It merely contrasts the reading of "positive" at one time and that of "negative" at another time. In order to answer the other two questions, those of *over-reading* and *under-reading*, it becomes necessary to determine which of the films in the set are "positive" and which are "negative." Since the problem relates to x-ray evidence of disease, criteria are needed for each of the films establishing whether it contains such. This information is obviously lacking. In the present study, arbitrary criteria had to be set up. These were of two kinds. The one defined a positive film on the basis of all the independent readings by the different observers which were available for the film. In other words, it was assumed that any film which had a majority of positive readings (four out of six) on it was probably positive, and, therefore, should not be called negative. Conversely, a film which had only one or at most two positive readings out of a total of six readings is probably negative, and therefore, should not be called positive. Such films as had exactly three positive and three negative readings were considered an "in-between" group and no demerit was scored against a reader who called such a film either positive or negative. The second method of deciding which of the test films were positive and which negative was obtained in conference. Several months after the independent readings were obtained, the group met and reviewed the films together. At this meeting discussion was allowed and the group as a whole arrived at a decision as to whether the film was positive or negative.[7] They had at this time no knowledge as to what they called the film in their previous independent readings. By either of these methods, therefore, it is possible to determine the films in the sets which are probably positive and those which are probably negative, and hence it is possible to obtain for each of the readers, as well as for the group as a whole, the percentage of positive films which were under-read and the percentage of the negative films which were over-read.

[7] Or attempted to do so. Even when in prolonged conference, the three readers could not always agree on whether a lesion was present, or whether a given shadow was significant.

The results did not differ much whether the first or the second criterion was used in defining positive films, if the same base was retained. In the second method, however, the "in-between" class is eliminated and therefore the readers lose the advantage of not being marked wrong on them. Consequently the under-reading score is higher when the second method is used. The results of this comparison are presented in Table III, which shows that the G. M. Z. group missed as many as 7 per cent of the positive films and over-read some 12 per cent of the negative films. The percentage for under-reading is encouragingly lower than that attained in the previous studies (which showed 17 per cent and 11 per cent, respectively). On the other hand, the over-reading percentage is higher than that of C. R. N. (10 per cent). It must, of course, be realized first that the material on which the different groups was tested may have been of different degrees of difficulty; also that the G. M. Z. group had the advantage of more frequent discussions than was true of the other groups. More important is the fact that in the comparison of G. M. Z. the group with exactly three positive readings was considered an "in-between" group and a reader was given credit whether he missed these or not. If this group is considered "positive" the percentage of under-reading almost doubles (13 per cent).

Special Comment: The reason for the relatively high percentage of *over*-reading is not known. It may be a function of the material sampled, or the conditions under which the tests were made (readers "straining" not to miss minimal lesions). We intend to check it on a test run of a large consecutive set of survey films, made under average conditions. The percentage of *under*-reading (or misses) is believed to be valid and indicative of the important problem at hand.

(*b*) *Reasons for Missing Lesions:* Considerable effort was exerted by the G. M. Z. group in attempts to determine the types of lesions which cause difficulty in "seeing lesions" and the reasons for missing them. The difficulties involved in such a study are numerous, and only the early stages of the analysis can be presented here. The group reviewed 99 films previously read, without knowledge of those previous readings. In conference, they classified each film as to whether it was positive and should be followed, or negative and should not be followed. In each case they also came to a joint agreement as to whether the film was easy to diagnose, difficult to diagnose, or "in-between." Such decisions were reached for both the positive and the presumably negative films. In either event, they expressed the group opinion as to why they thought a lesion was easy or difficult of diagnosis. These results were then correlated with their previous readings.

TABLE IV: EVALUATION OF GROUP DECISION ON "EASE" OF DIAGNOSIS

Percent of Under-reading of Positive Films and of Over-reading of Negative Films, According to Group Decision on Ease of Diagnosis on a Set of 99 Films

Group Decision on Ease of Diagnosis	"Positive" Films		"Negative" Films	
	Number of Films	Percentage Under-read	Number of Films	Percentage Over-read
Easy	29	2.4	18	11.5
In-between	5	13.8	20	22.8
Difficult	12	33.3	15	26.7
Total	46	11.7	53	20.0

The extent to which the group was able to characterize a film as being easy of diagnosis can be judged from Table IV. From this table, it appears that there are special characteristics which make for ease or difficulty of diagnosis, and that at least this group of readers was able to prognosticate which film would be easy, which would be very difficult, and which mildly difficult. This can be judged from the fact that out of all the positive films which the group thought were easy of diagnosis only 2 per cent were called negative in the previous independent readings. Of those positive films which the group called "in-between" 14 per cent were previously missed, while of those considered difficult fully 33 per cent were missed in the previous independent readings. Similarly, for

TABLE V: APPARENT REASONS FOR SEEING OR MISSING LESIONS (PRELIMINARY TRIAL)

Findings on 99 Films, as Reported in Group Conference of Three Readers, the Films Being Classified as Probably "Positive" or "Negative," and Also as Being "Easy" or "Difficult" to Interpret

Reasons Given	"Positives"		"Negatives"	
	Easy	Difficult	Easy	Difficult
Location*	26	8	1	..
Size	20	..	..	1
Density	12	..	2	..
Textbook (classical)	1	..	4	..
Resembled vessel or muscle shadows	..	7	..	21
Faintness	..	11	..	3
Artefact	..	4	..	2
Interpretation	..	5	1	..
Poor film	..	2	..	5
Good film	..	..	4	..
Other	1	1	..	7

* This usually means that the shadow was in an interspace when "easy," and either hidden by a rib or located at a base when "difficult."

those films called negative by the group, the ones considered easy of diagnosis were previously over-read in 12 per cent of the cases, the "in-between" negatives had a 23 per cent over-reading, while the difficult negative cases were previously called positive in 27 per cent of the cases. It is also evident from this table that it is more difficult to read a negative film than a positive. Thus, of the total 53 negative films in the set, the group considered only 18, or one-third, as easy of diagnosis, while of the 46 positive cases, the group considered 29, or nearly two-thirds of the number in the same category.

The reasons given by the group either for the ease or for the difficulty of diagnosis are shown separately for the positive and negative films in Table V. On the positive films, three main groups of reasons were given for considering a film easy of diagnosis; first, *location*, that is the lesion was in the upper part of the lung and, roughly, in an interspace; second, *size*, the larger lesions being usually easier of detection; third, *density*. The reasons for difficulty in detecting positive films as expressed by the group were more numerous. A considerable number of them can be characterized as those in which the lesion is hidden by or merges with a rib, heart shadow, or the like; where it is faint or is of slight density, or is difficult of interpretation, meaning that it might be mistaken for a vessel or an artefact. For the negative films, good quality of the film was probably the predominant reason for ease of diagnosis. Negatives which were difficult of diagnosis would be those which contained what were considered to be extraneous shadows, as muscle shadows, heavy vascular markings, or scars, or those of poor technical quality. As was stated above, further analysis of these reasons and their correlation with the actual performance of the readers in detecting lesions are being continued. One obvious deduction from the above table is that at least a part of the difficulties in diagnosis, particularly in over-reading of negatives, can be reduced by improvement in the quality of the roentgen image.

(*c*) *Methods of Interpretation:* In its more comprehensive form, the study on methods of interpretation involves, as was stated above, many areas of science and includes such considerations as the psychological and physiological, not to mention the philosophical and semantic, phases of the problem. The G. M. Z. group has not yet reached the stage where a really serious attempt has been made at investigating the methods of reading films and their effect on "seeing a lesion." However, they accidentally stumbled on one minor phase of this problem which produced sufficient results to warrant reporting, if only for the sake of stimulating others to attempt investigation thereof. This phase concerns the *attitude* of the reader and its effect on missing a lesion.

In the initial meetings, after the group had arrived at joint decisions on methods of interpretation, it was agreed that when in doubt whether the film was positive or negative, the reader was to assign to each probable lesion the "worst possible prognosis" (to call a shadow positive whenever in doubt). It was discovered, however, when the readings were analyzed, that only one of the group followed the instructions literally on this score, while the others did

TABLE VI: EVALUATION OF ATTITUDE OF READER ON DETECTING A LESION

Number and Percentage of Under-Reading (False Negatives) and Over-Reading (False Positives) on 225 Films Diagnosed To Be "Positive," "Questionable Positive," and "Negative" on the Basis of a Majority Group Decision by Three Readers

Group Opinion on Films	Of 87 "Positives" Obtained in Group Decision by 3 Readers (with 261 Expected "Positive" Readings)		Of 9 "Questionable Positives" in Group Decision by 3 Readers (with 27 Expected "Positive" Readings)		Of 129 "Negatives" Obtained in Group Decision by 3 Readers (with 387 Expected "Negative" Readings)	
	Results Obtained in Independent Readings According to		Results Obtained in Independent Readings According to		Results Obtained in Independent Readings According to	
	Best Possible Prognosis	Worst Possible Prognosis	Best Possible Prognosis	Worst Possible Prognosis	Best Possible Prognosis	Worst Possible Prognosis
Number of recorded "positive" readings	221	235	6	10	18	27
Number of recorded "negative" readings	40	26	21	17	369	260
Percentage of under-reading	15.3	10.0	77.8	63.0	...	...
Percentage of over-reading	...	...	...	...	4.7*	7.0*

* See footnote to Table III.

not. As a consequence, this reader selected a relatively larger number of positives than did the other two. On further analysis, when the readings of each member of the group were compared with the combined judgment of his two colleagues on each film, it was noted that this reader missed none of the films which were called positive by both of his colleagues on each of the four readings. On the other hand, each of the other two men did miss a few of the films which were selected as positive by both his other colleagues.

It appeared to the group that it was worth while following up this lead in order to determine if it was really the attitude (that of giving each probable lesion the worst possible prognosis) that was responsible for this accomplishment. In other words, is it possible intentionally to over-read in such a way that one reduces the number of misses on the truly positive films? This is not, as it appears on first blush, an obvious deduction, for certain previous attempts at solving this problem did not produce the desired results. In other words, mere over-reading does not necessarily lead to a reduction in under-reading. The over-reading needs to be systematic. In studying the problem, the group was very conscious of the penalty in the form of over-reading which must be paid for the advantage of a reduction in under-reading. A method was therefore sought which would accomplish the desired result in terms of under-reading without unduly increasing the over-reading percentage. The last technic that was tested appears to be a beginning in the right direction. This method is as follows: The reader attempts first to review all the films with a pessimistic attitude. In this process he separates the films into two piles, one containing those which he believes are *definitely negative,* the other containing as nearly as possible all the positive and questionable films. This second pile inevitably contains also a number of negative films. The reader then takes a "second look" at each of the positive films, but this time he is very critical and attempts to select only those that he actually believes are positive, while those that he thinks are negative he rejects from the pile (that is, a very optimistic attitude).

In order to test whether this method would succeed in missing fewer of the real positives and yet not produce too many false positives, a set of 225 films was selected and circularized twice among the readers. In the initial round the readers were instructed first to screen the films by their usual method (that is, not attempting consciously to give each lesion the worst possible prognosis) and divide them into two groups, positive and negative; the

positive group was then re-read very critically and only those which were considered really positive were retained as such. On the second round, the same films were initially screened with the attitude of giving each lesion the worst possible prognosis. The positives and questionables selected by this screening were then reviewed in the same critical manner as on the first round. The numbers of positive films missed by the two methods of reading were then compared. It should be noted that such differences as will be found between the two methods are due entirely to the *attitude* of the reader on the initial reading, since the same critical review was employed in both rounds.

The results of these tests are shown in Table VI. The method of comparison in this table is as follows: The 225 films were first reviewed by the three members of the committee in conference (after a lapse of some time subsequent to their independent readings and without knowledge of their previous readings). The conference then reached a conclusion on each film as to whether it was positive and should be selected for follow-up, or was negative and should not be called back for follow-up, or was in an in-between group labeled "questionable positive." The results of each of the three members' previous readings by the two methods were then compared for the positive films, questionable films, and negative films. It was found that each of the members of G. M. Z. missed fewer of the positives by the second (pessimistic) method of reading than by the first or the normal method of reading. On the 87 films which were presumed to be positive the three members together had a total of 40 negative readings by the first method and only 26 such negative readings by the second method. In terms of percentages, the first method of reading missed $\frac{40}{(3 \times 87)} = 15.3$ per cent as compared with $\frac{26}{(3 \times 87)} = 10.0$ per cent for the pessimistic approach. Similarly, on the 9 films that were selected by the conference as questionably positive, there were a total of 21 negative findings by the first or optimistic reading and only 17 by the second. In terms of percentages, there were $\frac{21}{(3 \times 9)} = 77.8$ per cent misses by the optimistic method and $\frac{17}{(3 \times 9)} = 63.0$ per cent misses by the pessimistic method. It therefore appears that *the attitude of the reader certainly does affect his ability to select the positive films.*

It now becomes important to determine what penalty is paid for this improvement. This can be measured in terms of the number of films considered by the group to be negative which were called positive by each of the two methods (over-reading). On the 129 films that were considered negative by group opinion, there were a total of 18 positive readings by the first method, while the second or pessimistic method produced 27 positive readings. In terms of percentages, the over-reading score by the first method was $\frac{18}{(3 \times 129)} = 4.7$ per cent, while for the second method the percentage was $\frac{27}{(3 \times 129)} = 7.0$ per cent. In other words, while the over-reading is greater for this pessimistic method of reading, it is not unduly so. Incidentally, it should be noted that the over-reading percentage is lower than the one given previously in Table III. This can be attributed to the "second look," since a reader had the opportunity of changing his mind and calling negative a number of those that he originally called positive. This technic of reviewing the positives might be a useful method in mass survey work even without the benefit of the pessimistic method of reading.

It may also be worth commenting that the comparisons shown above do not represent the entire benefit resulting from the "pessimistic method of reading," since it was found that a relatively large number of those films which were missed during the pessimistic trial were not missed completely, but rather were selected during the pessimistic screening and were called negative on critical review. When a comparison is made between the two methods of reading, on the basis of *complete misses*, where the case was called negative initially, the ordinary method of reading produced

29 negative readings whereas the pessimistic method of reading produced only 7 negative readings on the 87 positive films. While this method has not yet been tested extensively, it did have one retest by the C. R. N. group. Although they did not have the benefit of indoctrination, as had G. M. Z., two of the members were able to duplicate the results; the third one did not on the straight comparison, although even his results were the same as those stated above on the basis of complete misses. It would be necessary for other groups to repeat such an experiment in order to verify or disprove these results.

Should the results be substantiated by other experiments, they would then become not only important as a possible lead to the psychological aspects of film interpretation, but they would also have a definite practical application. It has been recommended that in mass survey work, the survey films be interpreted independently by two different specialists. Few of the agencies conducting mass survey work have to date implemented this recommendation. The reason usually offered is the shortage of competent interpreters. If the above method can be perfected, it may be possible to attain almost as good results by a single pessimistic reading with a critical review of only the positive films. To be sure, a number of practical difficulties will arise, particularly in finding an easy way of separating, in mass survey work, the positive films encountered in a roll to afford an easy method of review. However, a simple marginal punch device could be attached to roll-film viewers, and the first run "suspects" marked accordingly. For non-roll film, mechanical sorting is simple.

Describing a Lesion

The G. M. Z. group did not neglect the second and more fundamental problem, that of describing a lesion. Throughout all the attempts of C. R. N. in this field, one thing stood out, namely that *the more categories or terms that were used in describing a lesion, the greater was the inconsistency* both among different readers and for the same reader with himself. In the face of this, the G. M. Z. committee decided in its initial attempts at the problem to allow for each characteristic only a limited number of descriptive terms or categories. For example, while attempts had been made to describe the texture of a lesion in any number of categories, such as homogeneous, honeycombed, spotted, stippled, streaked, and the like, G. M. Z. came to the conclusion that it is impossible for any two readers, or for any one reader twice, to be consistent in such a description. G. M. Z., therefore, allowed a reader to describe the texture of a lesion in only two ways, uniform or not uniform. For this reason, their results naturally show considerably greater consistency in this field, but the descriptions are too coarse to be useful.

In presenting the results of description by G. M. Z. it is not our intention to convey the impression that something positive has been attained. Rather, it is the sharing of labor pains in this very difficult problem with the hope again of stimulating research by other workers.

The following seven terms were utilized in description: location, shape, size, orientation, density, sharpness, and uniformity. Since location was marked on each film, this was not tested, leaving the following (see also Fig. 3):

1. Shape (rough, geometric terms)
2. Orientation (*i.e.*, whether directed toward the hilum or otherwise)
3. Size (of entire lesion, or of each principal lesion)
4. Density (slight or marked, or combinations)
5. Sharpness of border (sharp or fuzzy, or combinations)
6. Uniformity (heterogeneous shadow or homogeneous shadow)

The results of the latest trial in using these symbols in describing lesions are shown in Table VII. In this trial the lesion was marked on the film by a radiologist not participating in the study, so that each reader read the same area. The description again was done twice inde-

Reader_____ Date_____ Set of Films_____

Reading: 1st _____ 2nd _____

Film No.	Shape (Triang., rect., circ. or oval, irregular)				Orientation of Long Axis (Clearly toward hilum or not)		Size (approx. max. length and breadth in cm.)		Density (marked or slight)				Sharpness (sharp or fuzzy)				Uniformity (uniform or heterog.)				Remarks
	△	□	○ ⬯	Irreg.	Toward hilum	Not T. H.	Length	Breadth	M	Ms	S	Sm	S	Sf	F	Fs	U	Uh	H	Hu	

Note: "Location" will be marked on the film. Record predominant features of the lesion. Note any deviation from these by checking appropriate columns.

Fig. 3. Second type of check sheet used by G. M. Z. See text.

TABLE VII: EVALUATION OF TERMINOLOGY USED TO DESCRIBE LESIONS

Number and Percentage of "Complete" Agreements and Agreements by Major Symbol (See Text) Among Three Readers (Inter-individual) and for Different Interpretations by the Same Reader (Intra-individual) on 75 Films for Six Fields of Description

	Of 75 Films Read by 3 Readers (with 223* Expected Agreements for Inter-individual Comparisons and 222† Expected Agreements for Intra-individual Comparisons), Results Obtained for									
	Density		Sharpness		Uniformity		Shape		Orientation	
	Inter-individual	Intra-individual	Inter-individual	Intra-individual	Inter-individual	Intra-individual	Inter-individual	Intra-individual	Inter-individual	Intra-individual
Number of recorded agreements										
Complete	118	148	114	159	127	168	146	172	146	186
By major symbol	185	191	173	189	180	200	...	...	...	...
Percentage of recorded agreements										
Complete	52.9	66.7	51.1	71.6	57.0	75.7	65.5	77.5	65.5	82.9
By major symbol	83.0	86.0	77.6	85.1	80.7	90.1	...	...	...	...

* Two readings not tabulated.
† Three readings not tabulated.

pendently by each reader, so that it was possible to obtain a measure of consistency between readers and for each reader with himself in using these descriptive terms.

A review of this table shows that, if held to specific categories, the degree of consistency is very low on most of the terms used. It is generally lower for *inter*-individual than for *intra*-individual comparisons. The best score, 82.9 per cent, was attained for *intra*-individual comparisons on orientation; the worst, 51.1 per cent, for *inter*-individual comparisons on sharpness. Bad as these scores are, they are better than those attained using multiple categories. On the basis of major symbols (*e.g.*, *M* not in disagreement with *Ms*), the scores are naturally much better, reaching 90 per cent for *intra*-individual comparisons on "uniformity."

These attempts at description are no doubt very feeble. The members of the committee confess that when they were on the sidelines, viewing the attempts of C. R. N., their results appeared incredible. At least two members of G. M. Z. had felt that *they* knew whether a lesion was homogeneous or not, whether it was fuzzy or sharply defined, and what its shape was ...but experience awakened them. Most radiologists reviewing the above table no doubt will have the same feeling. After a few months of struggling with the problem, the present committee is convinced that it is a most difficult and a major problem facing radiology. Colleagues agnostic will greatly benefit by a serious systematic attempt at describing the shadows that they see on an x-ray film.

DISCUSSION

When physicians disagree with each other and with themselves on the interpretation of roentgenograms in an appreciable percentage of cases, it is noteworthy. When this phenomenon is found to occur in diverse portions of the country, it demands investigation, even though it be of lesser magnitude than that found in other medical problems.

The first reaction of every new observer is: "This does not happen to me." To these, we suggest: "Try it systematically."

The reasons for the variations are baffling and have been subjected to much study, radiological, visual, psychological, and philological. "To behold," said Wm. Humbolt, "is not necessarily to observe; the power of comparing and combining is only to be obtained by education." Some of the reasons are related to the difficulty inherent in any recording medium—failure to reproduce clearly small lesions, introduction of artefacts, and the like. Many of the errors are due to the personal equation—there are times when an expert "sees"

a "seeable" lesion clearly and times when he doesn't. There are times when he overreads a normal shadow and times when he doesn't. That this should happen to amateurs is accepted, but that it should happen to experts is now for the first time thoroughly proved statistically.

This fact is no reason for deprecating either the experts or the method. The pioneering group of the former is to be congratulated for their intrepidity in such searching analysis. The method itself is to be complimented for the relative accuracy obtainable with its intelligent use. But more is needed if we are to attain the degree of perfection so greatly to be desired. That "more" is a problem facing all physicians. It can be approached by periodic statistical analysis of medical procedures, both diagnostic and therapeutic.

Bacon, in his *Novum Organum*, divided fallacies into 4 idols (or false appearances) which summarize the various kinds of mistakes to which the human intellect is prone. The *Idola Tribus*, or idols of the tribe, are fallacies inherent in human kind in general (notably man's proneness to suppose in nature greater order than is actually there). The *Idola Specus*, or idols of the cave, are errors inherent in our individual constitution, our private and particular prejudices, as it were. [Both physicians and statisticians manifest these at times!] The *Idola Fori*, or idols of the market-place, are errors arising from the influence of mere words over our minds. Finally, the *Idola Theatri*, or the idols of the theater, are errors arising from received systems of thought.

The intent physician is constantly on the alert to combat these very human fallacies. To remind himself of their existence, he must subject himself to reflection and analysis, and must submit his conclusions to periodic critical evaluation. This evaluation will reveal a certain percentage of error in all our work. A professor of medicine once said: "See how inaccurate radiological work is. The experts cannot read the same film twice in agreement with themselves or with one another." Alas, if he tested himself on some accepted clinical medical procedure, would he not find a comparable or higher degree of error? Chesney (5) observed: "It is not the particular form of postgraduate education that a doctor elects to pursue that matters so much, as whether the students we graduate leave us with the desire to continue as students of medicine for the remainder of their lives." Many of the members of the Radiological Society have this desire and for that reason will be interested in subjecting themselves to what is really an analysis of their scientific ability. As the result thereof, they may evolve steps to increase their accuracy and ability in detecting disease in ever earlier and more curable stages. A most valuable by-product of such tests will be renewed recognition of personal variability, which will make us more critical of our own work and more tolerant in appraisal of that of others.

If our method of testing diagnostic efficiency is sound, then our next steps must be (*a*) the development of a simple reliable descriptive terminology for roentgen shadows, (*b*) an evaluation of present standards for determining activity and prognosis, (*c*) a reliable classification of pulmonary tuberculous lesions.

Possible Methods of Improvement

By what means can the interpretation of films be made more accurate? The first and most obvious method is by better training of and periodic testing of radiologists and other physicians engaged in this work. The next appears to be double reading by two different observers, or review reading of "probable positives" by the same observer. These two methods will now be considered.

The Value of Double Reading by Two Observers: In applying to mass-survey work the results of the variation in film interpretation, their significance looms very large. It could be assumed that the average reader of mass-survey films is not much more acute in detection of positive films than are the members of these boards. Consequently, every day many persons throughout the

country are being informed that their chests are free from disease when, in point, of fact, they probably are not (and vice versa). This results in false security on the one hand and needless alarm on the other. It is, therefore, of extreme importance for agencies conducting such surveys to take as many precautions as possible to reduce the amount of error. One solution is to have every set of survey films interpreted independently by two readers. Such a procedure will reduce the number of positive films missed. On theoretical grounds it can be argued that if an individual reader will miss as many as 20 per cent of the positive films, then, if the same films are interpreted by two such readers, only 4 per cent of the positive films will be missed. However, this theoretical argument may not hold, since it assumes that every positive film is as likely to be missed as any other such film, and that each reader is as likely to miss as many of the positive films as any other reader. Results, to be published elsewhere, can be utilized for an estimate of costs involved, and show that dual reading is an economical case-finding procedure. In other words, it would cost more to find by a new survey a number of cases equal to those discovered by the dual reading than is involved in the cost of an additional reading.

The Value of Review Reading by a Single Observer: This has already been discussed in the report of G. M. Z. studies (see above).

The Technic of Reading Films

When the practising radiologist is confronted with the findings noted in this and comparable papers, his first reaction is "*I* don't make that degree of error," and his next is "*If* they read the films slowly and carefully they wouldn't make those errors." As to the first opinion: a statistically valid test will soon remove his illusion and restore his normal scientific reserve. As to the second: slow and careful interpretation *should* be the answer, but has not proved to be so in our hands. In discussing the problem, we asked two of the radiologists with the highest scores for accuracy to describe their methods of reading chest films, and we record them herewith.

It is to be realized that the description of any inspection procedure usually makes it seem much more lengthy than it actually is in practice. A "positive" film (*i.e.*, one with obvious shadows of disease) can be read for survey purposes in a few seconds; a "negative" film takes considerably more time; a "questionably negative" one requires up to five or ten minutes of study, especially when a reader is fatigued.

Method of L: The interpreter examines in rapid succession the following shadows: heart, aorta, mediastinum, diaphragm, cardiophrenic, and costophrenic sinuses. He then compares apex with apex, first space on the right to first space on the left, and so on down to the diaphragm. He then examines the shadows "on" the posterior ribs on the right; then those "under" the anterior ribs on the right. Similarly the posterior ribs on the left; and then the anterior ribs on the left. Finally he surveys the extrathoracic soft tissues.

Method of R: The interpreter examines the central cardiovascular shadow. Then he allows his eyes to "sweep" over both lungs for radiability, etc. The eye follows the periphery of the lung from the costophrenic angle up to the apex, then down along the paramediastinal area and back to the starting point. Next, the film is examined, intercostal space by intercostal space, from apex to base on the right, and likewise from apex to base on the left. Finally, individual spaces are compared for differences in density, right side and left, apices to bases.

The study group discussed different methods in conference. Some experienced radiologists felt that they used no fixed technic. Others said that they used the system of expanding circles, *i.e.*, they interpreted a film in a series of circular inspections from the center to the periphery. Some did the reverse! Most admitted that, while they tried to use one consistent technic, they often varied from it, especially when distracted by some dominant or unusual finding.

It is our impression that a satisfactory system would be one in which the interpreter inspected first the central cardiovascular shadow and then the lungs, right and left, as a whole. Then he would require his eyes to follow each lung field, space by space, from apex to base; then rib by rib from base to apex. Next he would "look

across" from space to space, comparing right and left sides, from apex to base. Finally, he would review the bony thorax and extrathoracic soft tissues for any apparent abnormality.

The viewing distance may be important. The reader's eyes must be at a relatively fixed distance when interpreting minifilms with film-viewers, but when reading 14 × 17-inch films, it is possible that a fairly standard eye-to-film distance should be adopted. To avoid eye-strain and "flicker," the reader should force himself to rest periodically by glancing elsewhere in the room or walking around a little. Some observers report that they can read an astonishingly large number of films per hour (*e.g.*, over 400) with as much apparent accuracy as others who can read only about one-fourth such number. Therefore, the frequency with which eye-resting periods should be taken must vary widely with the individual.

Some readers have "blind spots" or affinity for certain types of lesions. For example, one interpreter will readily detect small fan-shaped lesions and distinguish them from branching blood-vessel shadows, while another will pass them up. The latter reader may then detect minute peripheral exudative lesions which the former reader will tend to miss. Therefore, some errors arise from lack of seeing the lesion, some from lack of correctly evaluating what is seen. It is our impression that when a reader attempts to "see and judge" simultaneously, his degree of error is greater than when he separates these processes. He should attempt to "see" first, and then attempt "judgment" on the significance, or otherwise, of the apparent abnormality he has seen.

Suggested Method of Testing Readers for Survey Work

Pending the development of some suitable test object, such as a pair of model lungs into which various known materials can be introduced and satisfactorily radiographed, we must use films of living persons. A test set should contain an adequate number of "positives" and "negatives" to permit statistical analysis. The "positives" may be films of persons who have been examined serially for several years, and whose shadows are known to correspond to areas of disease, or may be films validated as positive on a series of tests and retests by a clear majority of experienced readers.

The first and most important tests may be done with large films; subsequent tests should include films of the size commonly read in surveys (4 × 5-inch, 70-mm. or 35-mm.).

The exact number of films needed for a test depends on the composition of those films and their apparent ease of interpretation (see Table IV). We have established, out of a group of 225 films repeatedly studied by our group, a set of 150 containing a known number of positives and negatives, the positives varying from minimal to advanced. The caliber of this set in terms of "ease" or "difficulty" of interpretation has also been established. With such a set, it is possible to test a reader or group of readers. If he misses more than an allowable number of the positives, or over-reads more than an allowable number of the negatives, he should not be used. By allowable is meant that number which, although exceeding the number scored by competent readers, could be expected to occur on the basis of chance alone. Its precise determination depends on the material sampled and requires the assistance of one versed in statistics.

Prior to further development of this test material, it is essential that the disturbing element of *over*-reading revealed in almost all these tests to date be solved. As previously mentioned, steps in this direction are now being taken, using standard consecutive (as opposed to selected) survey material. The basis for the designation of "negative" cases is always open to debate, but can be refined by very large numbers of readings plus correlation with other data.

SUMMARY

1. It is established by this and previous work that the interpretation of roentgenograms is subject to a certain degree of inherent error.

2. The degree of error or variation is significant, but compares favorably with that found in other clinical methods and diagnostic aids.

3. The usefulness of studies on this phenomenon may be measured by the degree to which they are aimed at understanding the reasons behind the variations and by the discovery of methods to reduce them.

4. The results reported here indicate that among the important reasons for "missing" a positive film are the size, location, and density of a lesion, plus the "attitude" of the observer. A review technic which permits a reader to scan each "preliminary" positive may significantly reduce the percentage of positive cases missed, without undue penalty from overreading.

5. For mass-survey work it would appear imperative (*a*) to select the panel of readers with great care, (*b*) to submit them to valid tests, and (*c*) whenever practicable to utilize dual reading.

6. Much work is needed on methods of describing lesions and on rational evaluation of existing classifications.

7. It is believed that the accuracy of chest diagnostic work will be enhanced as a result of basic studies of the type outlined in this report.

ACKNOWLEDGMENT: To Drs. W. E. Chamberlain, Leo Rigler, and Robert Newell, the original C. R. N. committee, we owe a debt of gratitude for permitting us to join them in this investigation. The inspiration of their work was our mainstay. To Drs. Merrell Sisson, Ira Lewis, and many other workers, we owe deep appreciation.

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SUMARIO

Valuación Científica de los Procedimientos de Diagnóstico

Este trabajo, que constituye el Discurso Presidencial pronunciado en la Trigésimacuarta Reunión Anual de la Sociedad Radiológica de Norte América en San Francisco de California en el mes de diciembre de 1948, contiene la reseña de un estudio emprendido por una comisión compuesta de tres radiólogos designados para investigar el problema planteado por la variación en las lecturas de las películas torácicas tomadas en las encuestas corrientes. Dicha comisión reemplazaba a otra anterior, cuyo estudio también se describe sucintamente.

Ofrécense las siguientes conclusiones:

1. Queda establecido por esta y anterior labor que la interpretación de las radiografías está expuesta a cierto error inherente.

2. El grado de error o variación es significativo, pero se compara favorablemente con el observado en otras técnicas clínicas y auxiliares del diagnóstico.

3. Puede apreciarse la utilidad de los

estudios dedicados a este fenómeno por la asiduidad con que traten de comprender las razones que motivan las variaciones y por el descubrimiento de técnicas que atenúen dichas variaciones.

4. Los resultados comunicados ahora indican que, entre las importantes causas que hacen pasar por alto una radiografía positiva, figuran el tamaño, situación y espesor de la lesión, más la "actitud" del observador. Una técnica de repaso que permita inspeccionar cada positiva "preliminar" puede rebajar considerablemente el porcentaje de casos desapercibidos, sin exagerar demasiado las lecturas.

5. Tratándose de encuestas colectivas, parece imperativo: (*a*) seleccionar con sumo cuidado el grupo de lectores, (*b*) someterlos a pruebas de competencia, y(*c*) utilizar un sistema de doble lectura, siempre que sea factible.

6. Se necesita mucha labor más acerca de los métodos empleados para descubrir lesiones y acerca de la justipreciación lógica de las clasificaciones actuales.

7. Parece que la exactitud de las obras de diagnóstico torácico se beneficiará por virtud de estudios fundamentales de la índole bosquejada en esta memoria.

Angiocardiography in Congenital Heart Disease of Cyanotic Type with Pulmonic Stenosis or Atresia

I. Observations on the Tetralogy of Fallot and "Pseudo-Truncus Arteriosus"[1]

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THE DIAGNOSIS of pulmonic stenosis and particularly of the anomaly known as the tetralogy of Fallot has become more important since the surgical treatment of this condition has been established. The operation described by Blalock and Taussig (6) consists of an anastomosis between one of the large systemic arteries arising from the arch of the aorta and the pulmonary artery on the same side. Potts, Smith, and Gibson (11) have described a variant of this procedure which accomplishes the same end, namely a side-to-side anastomosis between the aorta and the pulmonary artery.

Before either of these surgical procedures may be undertaken, certain criteria must be fulfilled: (*a*) a pressure gradient between the systemic circulation and the pulmonary circulation sufficient to allow a satisfactory flow of blood into the pulmonary artery after anastomosis, (*b*) a pulmonary artery of sufficient size to permit an anastomosis on the selected side of the body, (*c*) a shunt of unoxygenated venous blood from the right to the left side of the heart. Some additional criteria are discussed by Taussig (20, *a*).

When employed in connection with routine clinical procedures in patients with congenital heart disease, conventional roentgenography gives information of great value in the diagnosis of pulmonic stenosis. Fluoroscopy is of special importance, as has been emphasized by Taussig (21, *b*). Decreased vascular markings in the lungs associated with a concavity of the upper border of the heart to the left of the sternum permits the inference that the pressure in the pulmonary arterial system is decreased. Occasionally, however, the pressure within the pulmonary arteries may be lowered distal to a point of stenosis despite an apparently normal vascular pattern in the lungs. If the point of stenosis can be demonstrated by direct visualization, one may assume that the pressure distal to this point is decreased. Conversely, in the absence of a demonstrable point of stenosis, the pressure in the pulmonary arteries might be expected to approach that of the right ventricle. Hence, a procedure which allows accurate visualization of the pulmonary conus and proximal pulmonary artery would be of considerable diagnostic value.

The pulmonary arteries may be visualized with a fair degree of clarity in normal subjects by conventional roentgenography. When the arteries are small, however, as may occur in the tetralogy of Fallot, estimation of their size or even the demonstration of their presence may be extremely difficult. It is in such instances that contrast visualization may be of great value. Although the degree of pulmonic stenosis can be estimated by cardiac catheterization and clinical methods, the presence or absence of adequate distal pulmonary arteries can only be suspected. Angiocardiography is peculiarly adapted to the solution of this problem.

A right-to-left intracardiac shunt of venous blood may often be inferred from such clinical studies as the circulation time and the presence of cyanosis at rest. More positive information, as well as measurement of the quantity of the shunt, may be

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[1] From the Department of Radiology and the Department of Surgery, the Johns Hopkins University and the Johns Hopkins Hospital, Baltimore, Md. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

achieved by cardiac catheterization and calculation of the flow of blood through the various vessels (3). In some instances, however, even physiological studies may leave room for further investigation. Angiocardiography may furnish additional diagnostic aid by direct demonstration of an intracardiac shunt in certain cases.

The presence of pulmonic stenosis, the character of the pulmonary arteries, and the presence of intracardiac shunts may be demonstrated by angiocardiography. This procedure comprises rapid injection of an opaque solution into the venous system, followed by a series of x-ray exposures to trace the progress of the solution through the heart and great vessels. Castellanos and his co-workers (7) employed this method in the diagnosis of congenital heart disease but failed to demonstrate the left side of the heart unless an intracardiac shunt were present. Robb and Steinberg (12, 13, 14) were the first to perfect a practical technic for angiocardiography which demonstrated all chambers of the heart. They visualized the left as well as the right side of the heart, the pulmonary vessels, and the aorta with its branches, both in normal persons and in those with various cardiovascular disorders. Steinberg, Grishman, and Sussman (9, 16, 17, 18) have used angiocardiography extensively in demonstrating congenital abnormalities of the heart and great vessels. Their studies include examples of the tetralogy of Fallot, the Eisenmenger complex, interauricular and interventricular septal defects, coarctation of the aorta, and patent ductus arteriosus. The role of this technic in evaluation of candidates for the surgical relief of cyanotic heart disease has not been thoroughly studied.

Recently we have employed angiocardiography in 75 patients with congenital heart disease of the cyanotic type, who were referred to us from the Children's Cardiac Clinic of the Harriet Lane Home, The Johns Hopkins Hospital. This group includes instances of tetralogy of Fallot, truncus arteriosus, pulmonary stenosis combined with tricuspid stenosis and atresia, complete transposition of the great vessels, the Eisenmenger complex, and many other anomalies which are difficult to classify. Certain advantages and certain limitations of the technic have been brought out during the study of these patients. In this communication we report our findings in selected cases of tetralogy of Fallot and "pseudo-truncus arteriosus," a condition to be discussed below. No attempt has been made to analyze the results in all cyanotic patients submitted to operation, but some helpful inferences may be drawn from the peculiar findings in individual cases.

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The tetralogy of Fallot is defined by Abbott (1) as a congenital malformation of the heart characterized by (*a*) pulmonic stenosis or atresia, (*b*) a dextroposed aorta overriding the interventricular septum, (*c*) a high interventricular septal defect, (*d*) hypertrophy of the right ventricle.

In this anomaly the infundibular portion of the right ventricle (conus arteriosus) is usually narrowed and deformed. The pulmonic valve may also be involved, although this is not regularly the case. Distal to the point of obstruction, the main pulmonary artery and its branches vary considerably in size, without constant relation to the degree of severity of the stenosis. In general, in the case of tetralogy of Fallot, the larger the aorta, the smaller is the pulmonary artery. In the case of tricuspid atresia and defective development of the right ventricle, however, the pulmonary artery usually approaches normal size (21).

Bing, Vandam, and Gray (4) found evidence of collateral circulation to the lungs in most of the 48 cases of tetralogy of Fallot which they studied. The amount of this circulation seems to vary with the age of the patient and with the degree of stenosis. The bronchial arteries are frequently enlarged, and there are large direct communications with the branches of the pulmonary artery (8). When pulmonary

atresia exists, the bronchial and other systemic arteries must be able to carry the entire circulation to the lungs unless there is a patent ductus arteriosus. Taussig (19) has described such a case and considers this condition a form of truncus arteriosus. We follow her present use of the term "pseudo-truncus arteriosus" in describing similar cases in this report.

In the tetralogy of Fallot, the degree of aortic overriding varies considerably. The aorta may originate almost entirely from the right ventricle, or it may approach its normal position and originate mainly from the left ventricle. The interventricular septal defect is usually quite high in the membranous septum beneath the mouth of the overriding aorta. Occasionally the defect is small and the degree of overriding is such that there is an obstruction to the outflow of blood from the left ventricle. This assumes added significance when the amount of blood entering the left ventricle is increased following the establishment of an artificial ductus arteriosus. Consequently it is felt that determination of the degree of overriding of the aorta and the size of the interventricular septal defect is of value in prognosis.

The over-all shunt of blood from the right to the left side of the heart has been measured (4) and found to vary considerably in different patients. Unless the defect is small or low in the septum, the shunted blood is swept out through the aorta without appreciable intracardiac mixing with the left ventricular blood.

TECHNIC

Our technic of angiocardiography is modified from that of Robb and Steinberg (12). In beginning this work, we were aided greatly by the advice and suggestions of Dr. George P. Robb. The patient is recumbent during the examination and multiple cassettes are used, with a special cassette changer. Since most of the patients are children, many with severe incapacity, a recumbent posture is preferred. This also facilitates the use of strong sedative medication, or of general anesthesia, which has been necessary on some occasions. The elevated diaphragm associated with recumbency has not materially interfered with the quality or interpretation of the films.

The cassette-changing device permits the making of six exposures in slightly less than five seconds. This is necessary because of the very rapid circulation time which obtains in most of these patients. Cassettes measure 11 × 14 inches, with provision for 14 × 17-inch cassettes when necessary.

Circulation times are determined in children with fluorescein and decholin, and in adults with decholin. Ether is used rarely, since most of the patients have a right-to-left shunt, in which case ether may have undesirable side effects (2).

A 70 per cent solution of diodrast is usually injected through the basilic vein of the left arm, although the external jugular vein is used occasionally in small children. Many of these children are too young to refrain temporarily from breathing or to inspire on command. This does not appear to be a serious handicap if the injection is given during the inspiratory phase of respiration and an exposure time of one-twentieth to one-thirtieth of a second is used. One cubic centimeter of diodrast per kilogram of body weight seems to be tolerated well by young children; slightly smaller amounts are given to older children and to adults. An intravenous test for sensitivity is always carried out, followed by an observation period of thirty minutes before the main injection is made.

Over 140 injections have been given to 75 patients with congenital cardiac anomalies of the cyanotic group. The ages of the subjects ranged from eight months to forty-two years. An immediate reaction, characterized by a feeling of intense heat over the entire body, has uniformly followed the injection, and an increase in cyanosis has occurred frequently. No serious reactions have been observed[2] ex-

[2] In a subsequent group of cases, one death occurred following three injections of diodrast within a short time. This child had a bizarre cardiac abnormality, which is to be reported.

TABLE I: SEVEN CASES OF TETRALOGY OF FALLOT AND TWO CASES OF PSEUDO-TRUNCUS ARTERIOSUS, SUMMARIZED

Case	Clinical Impression	Obscure Features	Angiocardiographic Findings	Physiological Studies	Findings at Operation
1. D. R. ♀ 4½ yr.	Tetralogy of Fallot	Course of aortic arch?	Aorta arches toward left and descends on left. Pulmonary arteries normal in size	None	Aorta on left. Pulmonary arteries of normal size, with decreased pressure
2. E. B. ♀ 16 yr.	Tetralogy of Fallot or Eisenmenger complex	Pulmonary arteries of normal size. Exercise test (5) suggestive of adequate pulmonary flow	Pulmonic stenosis not demonstrated, although pulmonary conus filled poorly	Definite evidence of pulmonic stenosis	Right pulmonary artery large but with low pressure
3. B. W. ♂ 14 yr.	Tetralogy of Fallot or Eisenmenger complex	Prominent pulmonary trunk and pulmonary arteries, apparently pulsatile	Pulmonary conus area not clearly demonstrated. Pulmonary arteries compatible with tetralogy	Definite evidence of pulmonic stenosis	Left pulmonary artery small with feeble pulsations
4. L. G. ♂ 22 yr.	Tetralogy of Fallot or Eisenmenger complex	Straight left cardiac contour. Prominent pulmonary vascular pattern	Area of stenosis strongly suggested. Pulmonary arteries of normal size. Left superior vena cava	Exercise test (5) suggestive of inadequate pulmonary flow	Left pulmonary artery of normal size. Pressure very low
5. R. A. ♂ 3 yr. 8 mo.	Tricuspid atresia or single ventricle? Patent ductus arteriosus	Continuous murmur. Globular heart. Left ventricular preponderance suggested by EKG	Not compatible with tricuspid stenosis or single ventricle. Pulmonic stenosis not clearly seen	Suggestive of pulmonic stenosis	Right pulmonary artery one centimeter in diameter and extremely flabby
6. P. D. ♂ 10 yr.	Atypical tetralogy of Fallot	Absence of systolic murmur. No right ventricular preponderance in precordial EKG leads	Marked stenosis. Pulmonary arteries fill through collateral vessels	None	Small right pulmonary artery without pulsations. End-to-end anastomosis performed satisfactorily
7. D. L. ♂ 4½ yr.	Probable "pseudo-truncus arteriosus"	No systolic murmur of pulmonic stenosis. To-and-fro murmur over base of heart and posteriorly. ? Presence of right pulmonary artery	Apparent atresia of pulmonic trunk. Right and left pulmonary arteries seem to fill through collateral vessels	None	Pulmonary artery "rather small"
8. S. S. ♀ 2¼ yr.	Possible "pseudo-truncus arteriosus" with large systemic artery to right lung	Continuous murmur over right side of chest. Retro-esophageal vessel. Presence of pulmonary arteries questioned	No evidence of a pulmonary trunk or left main pulmonary artery. Medium sized artery in right hilum	None	Proximal portion of right pulmonary artery obliterated. Retro-esophageal systemic vessel entered right lung. No artery on left at autopsy
9. A. P. ♀ 7 yr.	Tetralogy of Fallot	No pulmonary artery found at operation on right side. Referred postoperatively to determine presence or absence of left pulmonary artery	No pulmonary trunk or pulmonary arteries demonstrated. "Pseudo-truncus arteriosus"	None	Right pulmonary artery atretic

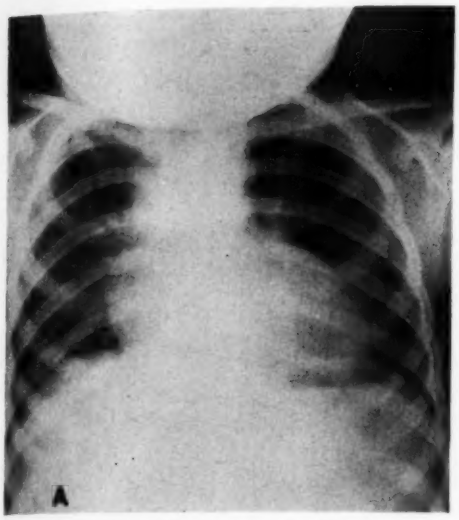

Fig. 1A. Case I. Plain roentgenogram, which shows that vascular markings are normal. The upper cardiac border to the left of the sternum is concave rather than convex.

cept in a twenty-two-month-old child who developed asthma which responded readily to adrenalin therapy. We do not regard the procedure as entirely innocuous, however, since fatalities have been reported (10, 15). The examination should be attempted only in those patients in whom there is likelihood of obtaining significant information. A summary of the nine cases reported here is presented in Table I.

CASE REPORTS

Seven instances of tetralogy of Fallot and two of "pseudo-truncus arteriosus" form the basis of this study. Each presented a problem in diagnosis for which an answer was sought in angiocardiography, combined with all other diagnostic aids. The angiocardiographic findings have been supplemented and clarified by physiologic studies (4), by operation, and in some instances by autopsy. A definitive evaluation of the results is thus possible.

CASE I: TETRALOGY OF FALLOT: D. R., a white girl, of four and a half years, was first noticed to be cyanotic at three weeks of age. A heart murmur was noted at two months. Development was retarded and there was marked limitation of exercise tolerance. On entry, the child showed the typical physical and laboratory findings of the tetralogy of Fallot. Conventional roentgenography (Fig. 1A) demonstrated the usual concavity along the superior border of the heart to the left of the sternum.

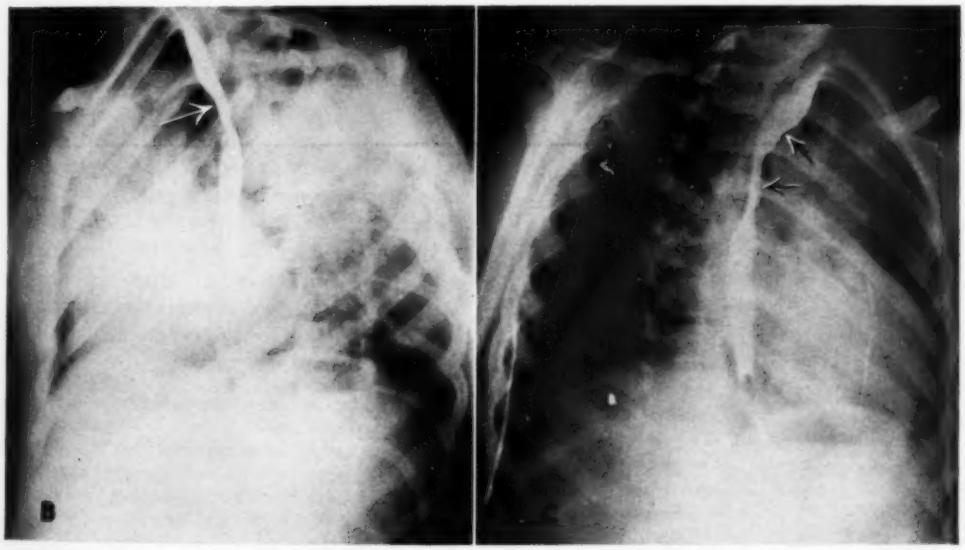

Fig. 1, B and C. Case I. B. Left anterior oblique view showing slight deviation of esophagus posteriorly due to aorta. C. Right anterior oblique view also showing aortic impression on left side of esophagus.

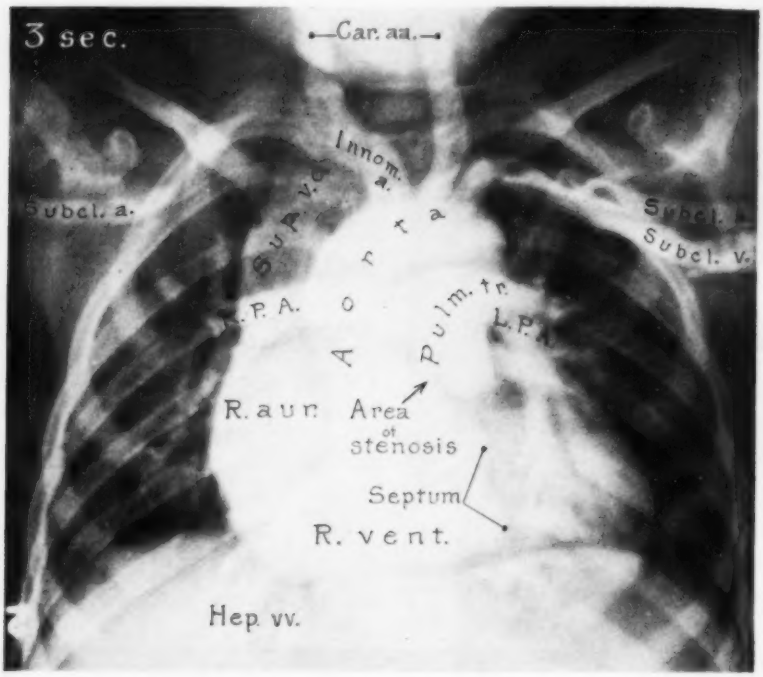

Fig. 2. Case I. Film made three seconds after beginning of injection (retouched to look like original). For description, see text.

The aortic impression on the esophagus, however, was anterior and only slightly to the left (Fig. 1B and C), and there was some uncertainty as to the course of the aortic arch. The patient was therefore referred for angiocardiography.

Angiocardiography: A film made three seconds after the beginning of injection (Fig. 2) shows most of the anatomic features of a tetralogy of Fallot. The aorta fills simultaneously with the pulmonary artery, and the left-sided course of the aortic arch is clearly demonstrated. The pulmonary trunk distal to the presumed area of stenosis is as large as normal for a child of this age. Forming as it does a portion of the left border of the heart, it might be interpreted from a conventional roentgenogram as incompatible with the diagnosis of pulmonic stenosis. The presence of stenosis in the pulmonary trunk is suggested, and the size and course of each pulmonary artery are demonstrated. The outline of the right ventricle in the coronal plane is also shown. At the upper portion of the interventricular septum there is a suggestion of leakage through the septal defect into the left ventricle.

At operation the right pulmonary artery was found to be normal in size but with low pressure and reduced pulsations.

Comment: In planning the surgical approach, it is essential to know the side on which the aorta descends. Occasionally doubt exists as to this point even after fluoroscopy. The aorta was accurately delineated here, as was the presence of adequate pulmonary arteries. An interventricular septal defect is shown by simultaneous filling of the pulmonary arteries and the overriding aorta.

CASE II: TETRALOGY OF FALLOT: E. B., a sixteen-year-old white girl, was slightly blue at birth, but the cyanosis was not definite until five months of age, when she had an upper respiratory infection. With the onset of walking she became dyspneic and had occasional fainting spells but was able to attend school and progressed normally for her age. At the time of admission she could walk a mile slowly and could climb one flight of stairs.

Physical examination showed a fairly well developed girl with only slight cyanosis. The heart was not enlarged and there was no arrhythmia. A moderately loud systolic murmur was heard just to the left of the sternum.

Fluoroscopy and conventional roentgenography showed a small quiet heart with a definite concavity in the region of the pulmonary trunk. Both pul-

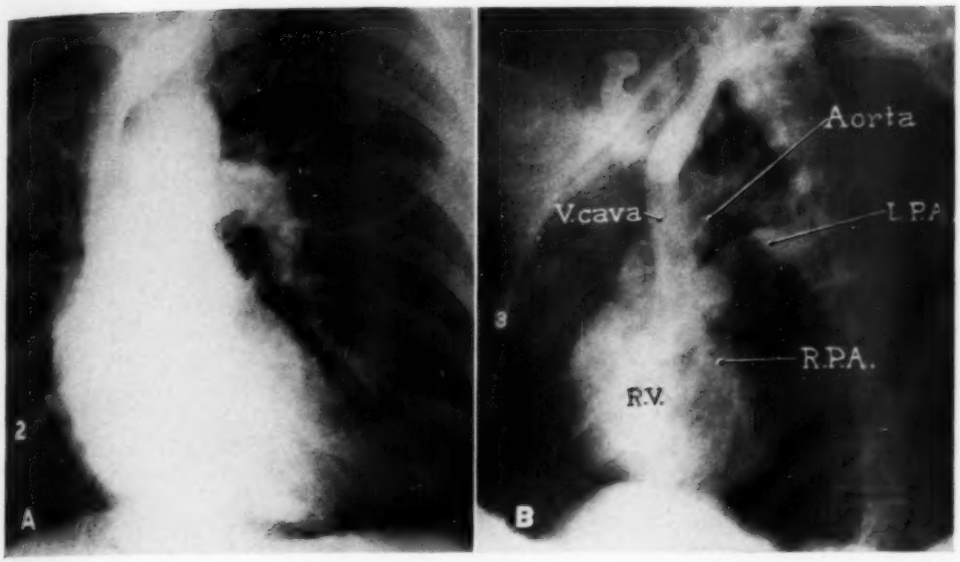

Fig. 3, A and B. Case II. A. Film made at the end of three seconds, showing normal vascular pattern in left lung and normal-sized left pulmonary artery. B. Right posterior oblique view showing superior vena cava, right ventricle, aorta, and right and left pulmonary arteries.

monary arteries appeared to be of normal size, although they did not pulsate. An exercise test showed an increased consumption of oxygen per liter of ventilation. This suggested the presence of an Eisenmenger complex (5) (dextroposition of the aorta, which overrides the interventricular septal defect, without pulmonic stenosis). Since the flow of blood to the lungs is unimpeded in the Eisenmenger complex, the establishment of an artificial ductus is contraindicated. The patient was referred for angiocardiography to aid in the differential diagnosis.

Angiocardiography: A film made three seconds after the beginning of injection in the anteroposterior projection (Fig. 3A) shows that the pattern of the pulmonary arteries in the lung, particularly on the left, is normal. In this view, there is insufficient penetration for visualization of the pulmonary conus. Simultaneous filling of the aorta and pulmonary arteries is well shown. A film made three seconds after injection in the right posterior oblique position (Fig. 3B) shows the superior vena cava, the right ventricle, the pulmonary arteries, and the aorta. The pulmonary arteries are normal in size and fill promptly. The infundibular region (conus arteriosus) is somewhat obscured, and one can say only that it fills poorly. Comparison with the excellent filling in a normal conus arteriosus (Fig. 3C) suggests that stenosis is present in the case under discussion, although we reported that stenosis could not be certainly demonstrated.

Cardiac catheterization, with insertion of the catheter into the pulmonary artery, showed a definitely decreased pressure distal to a point of stenosis. At operation, the right pulmonary artery was described as "a large but flabby structure" with a definite reduction in internal pressure.

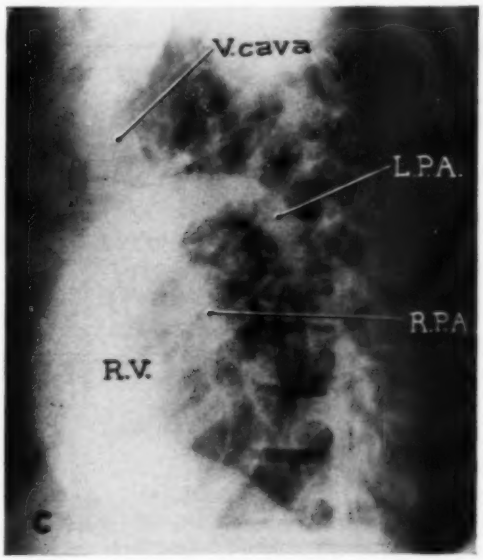

Fig. 3. C. Right posterior oblique view showing outflow tract of right ventricle and pulmonary arteries in a normal person, for comparison with a similar view in Case II (Fig. 3 B).

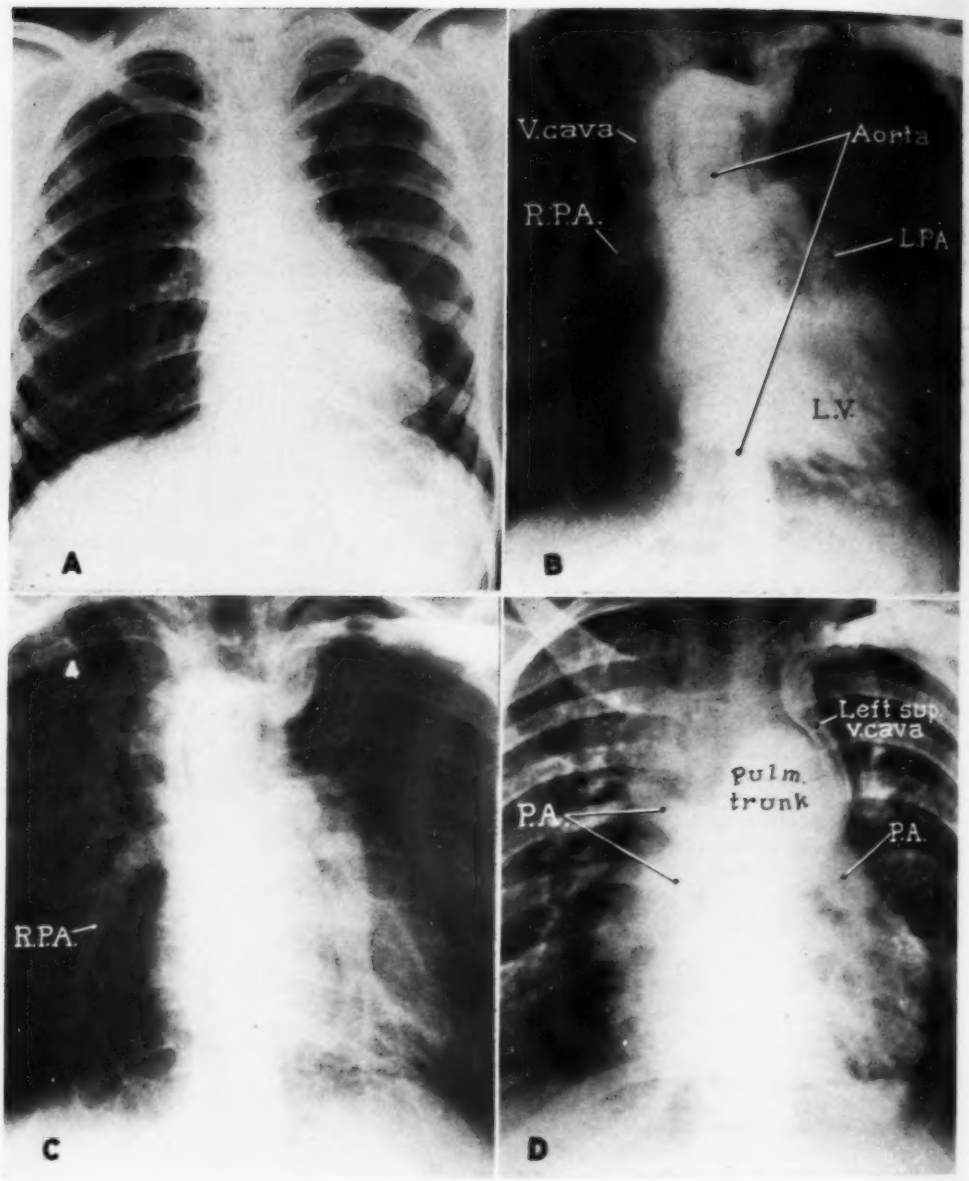

Fig. 4. A–C. Case III. A. Plain film. Cardiac silhouette is not significantly abnormal. There is no concavity of the left border.

B. Film made three seconds after injection. Contrast solution has entered left ventricle, apparently through an interventricular defect. The region of the pulmonic conus is obscured.

C. Film made four seconds after injection. Branches of pulmonary arteries are well demonstrated, but the conus is not well opacified.

D. Eisenmenger complex, for comparison. The tremendous pulmonary artery and its branches are shown in this reproduction of a film made four seconds after injection. There is a left superior vena cava.

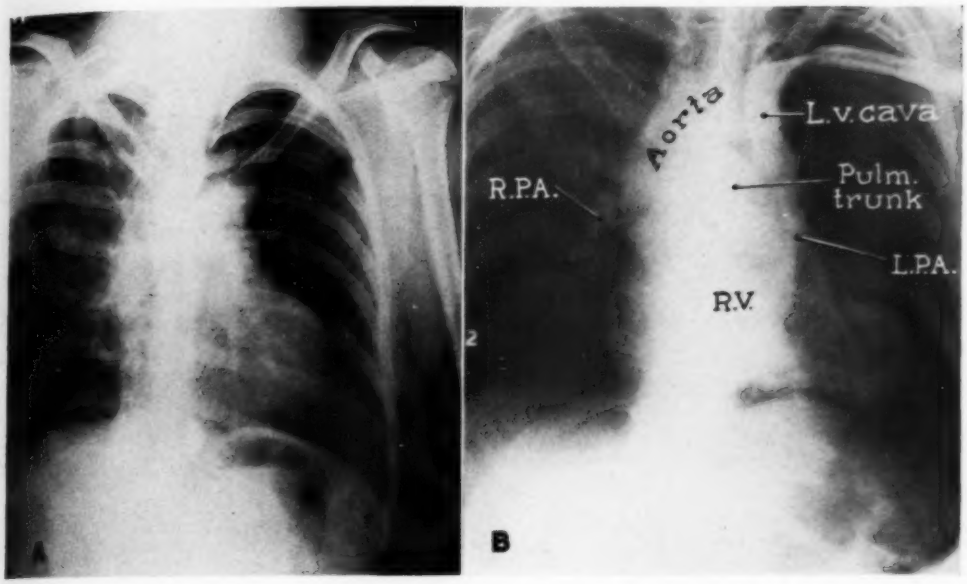

Fig. 5. Case IV. A. Plain film. Patient is slightly rotated, due to kyphoscoliosis. Concavity in region of pulmonary artery is not well marked. B. Film made two seconds after injection. Left-sided vena cava, right ventricle, and a good-sized pulmonary trunk are demonstrated; the area of stenosis in the conus is suggested.

Comment: Direct visualization of the site of pulmonic stenosis is difficult, and an angiocardiographic impression of "pulmonic stenosis" may be based on failure to demonstrate the normal contour of the conus. This is admittedly uncertain when such an area may change markedly during the cardiac cycle, giving an impression of stenosis due merely to periodic infundibular contractions. However, one would be unlikely to confuse the outline of the normal conus arteriosus (Fig. 3C) with that of a stenosis, and the conus arteriosus in an Eisenmenger complex would differ even more distinctively from that of a stenosis.

CASE III: TETRALOGY OF FALLOT: B. W., a fourteen-year-old white boy, was first observed to be cyanotic at one year of age, although heart disease had been diagnosed at birth. At the time of admission he could walk about five blocks and could climb one flight of stairs. There were occasional spells of "blacking out." Physical examination showed slight cyanosis, with moderate clubbing of the fingers and toes. The heart action was regular and the heart was not enlarged. There was a harsh systolic murmur, which was maximal over the left chest anteriorly at the level of the second interspace.

The conventional film (Fig. 4A) shows no cardiac enlargement. At fluoroscopy the region of the pulmonary trunk in the left contour of the heart was prominent and was thought to be pulsatile. There was a right aortic arch. The question presented at the time of angiocardiography was whether the patient was suffering from an Eisenmenger complex or a pulmonic stenosis.

Angiocardiography: A film made in the anteroposterior projection (Fig. 4B) three seconds after injection shows the pulmonary arteries well filled and approximately normal in size. The right ventricle is outlined but not so distinctly, since a considerable amount of the contrast solution has entered the left ventricle through a septal defect. This unfortunately obscures to a considerable degree the region of the pulmonary conus. This occurs also in a film made one second later in the anteroposterior position (Fig. 4C). Moreover, the root of the right-sided aorta obscures the conus area. A statement as to the presence or absence of infundibular stenosis is not permitted from the films. The size of the pulmonary arteries is entirely compatible with the presence of a tetralogy of Fallot.

Cardiac catheterization showed a definitely decreased pressure in the pulmonary artery distal to a point of stenosis. At operation the left pulmonary artery was smaller than normal, with very feeble pulsations.

Comment: The demonstration of the

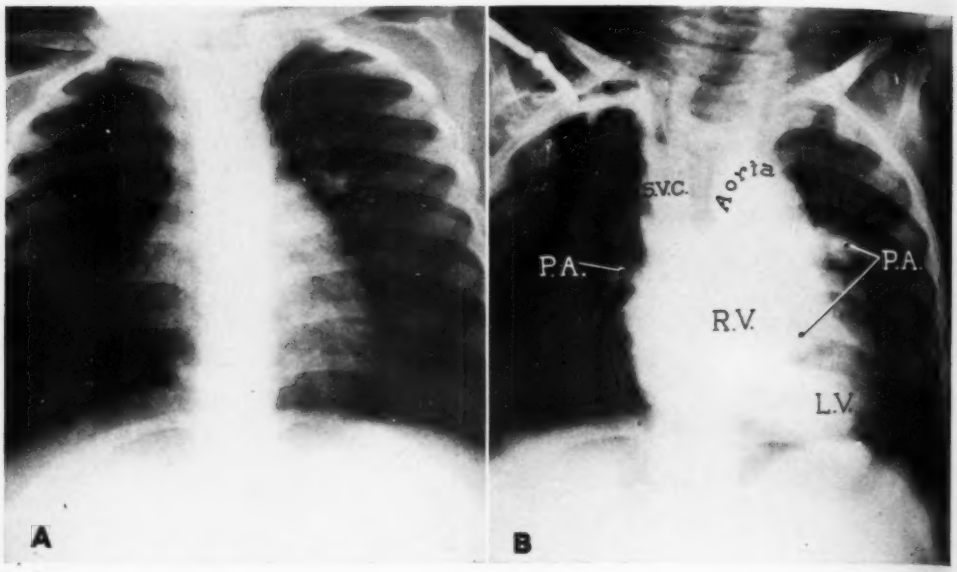

Fig. 6, A and B. Case V. A. Plain film. Contour of the heart is globular and does not suggest a tetralogy of Fallot. B. Film made three seconds after injection. The right auricle, right ventricle, and aortic arch are demonstrated, as well as a large vessel in the hilum of the left lung. Contrast solution enters the left ventricle apparently through an interventricular septal defect.

point of pulmonic stenosis by means of these films was not possible. However, there was no pronounced dilatation of the pulmonary conus and arteries such as might be expected with the Eisenmenger complex. An example of this latter condition is seen in Fig. 4D, showing the immense pulmonary trunk and large pulmonary arteries.

CASE IV: TETRALOGY OF FALLOT: L. G., a twenty-two-year-old white man, had been cyanotic since birth and dyspneic since he began to walk. He squatted frequently. At the time of admission he was able to walk three to four blocks under favorable conditions.

Physical examination showed severe underdevelopment. The heart was at the upper limits of normal in size. There was a short systolic thrill in the third interspace to the left of the sternum, and a blowing, high-pitched systolic murmur could be heard over the entire precordium, maximal in the pulmonic area, but transmitted to the neck and axilla.

Conventional roentgenography (Fig. 5A) and fluoroscopy showed the left heart border in the region of the pulmonic trunk to be fairly straight. The pulmonary arteries and vascular pattern in both lung fields were prominent. Because of this, the patient was referred for angiocardiography.

Angiocardiography: In a film made in the anteroposterior projection at the end of two seconds (Fig. 5B) a superior vena cava is seen on the left side. The right auricle is faintly outlined. The right ventricle, pulmonary trunk, and aorta are well demonstrated. The root of the aorta is of good size. The presumed area of stenosis in the outflow tract of the right ventricle is outlined. The pulmonary trunk distal to this point is normal in size, as are those portions of the pulmonary arteries which are seen. A report of tetralogy of Fallot with a left-sided vena cava was made.

At operation on the left side, a pulmonary artery of normal size was found, with reduced pressure. The left-sided superior vena cava joined what appeared to be a left inferior vena cava which looped over the lung hilum to form a large vessel which entered the right auricle.

Comment: A large left-sided vena cava may give a confusing cardiac contour. A diagnosis of pulmonic stenosis was made with reasonable certainty in this patient.

CASE V: ATYPICAL TETRALOGY OF FALLOT: R. A., a white boy of three years and eight months, had become cyanotic at nineteen months of age, when he began to walk. Cyanosis and marked incapacity persisted until the age of three years and five months. In the few months preceding admission, however, he showed remarkable improvement and actually learned to run.

Physical examination showed a slightly dusky cyanosis and moderate clubbing of the fingers and toes. The heart action was regular. A slight thrill could be felt in the first interspace just to the left of the sternum. In the first and second interspaces just to the left of the sternum there was a continuous grade-three murmur which was transmitted outward toward the axilla.

Fluoroscopy showed that the heart was not enlarged and that the contour was globular. A conventional film (Fig. 6A) confirms this. The left border is rather straight and the configuration does not resemble a tetralogy of Fallot. The electrocardiogram showed a left axis deviation, and unipolar precordial leads suggested a left ventricular preponderance. Because of this, the question of a tricuspid stenosis with a single ventricle arose, and the patient was referred for angiocardiography.

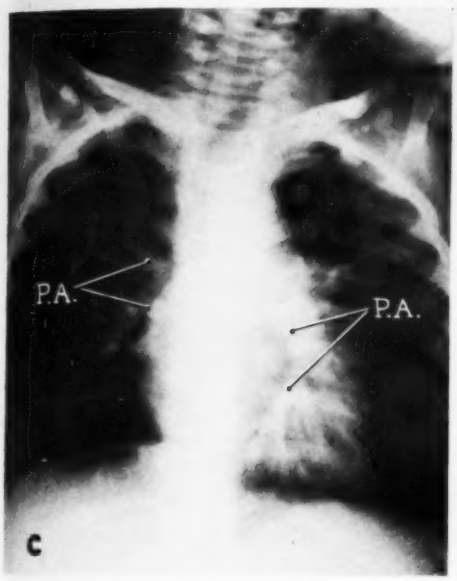

Fig. 6C. Case V. Film made four seconds after injection, showing contrast medium in branches of the large left pulmonary artery. A smaller right pulmonary artery is also seen.

Angiocardiography: In a film made three seconds after injection, in the anteroposterior projection (Fig. 6B), the contrast solution is seen in the right auricle, right ventricle, and aorta. There is definite increase in density of the left pulmonary artery, which appears more prominent than the right. A considerable amount of the contrast solution has entered the left ventricle. The interventricular defect appears to be large. Another film, made four seconds after injection (Fig. 6C), again demonstrates a large artery in the left hilum and a less prominent artery on the right. The pulmonary trunk is not demonstrated, and the region of the infundibulum cannot be identified with certainty. We reported that the left pulmonary artery was larger than the right and that there was an overriding aorta with a septal defect.

Fig. 7A. Case VI. Reproduction of conventional roentgenogram of chest. Heart does not have typical appearance of a tetralogy, and left border is straight.

Cardiac catheterization gave evidence suggestive of pulmonic stenosis. The right ventricular pressure was quite high and the oxygen content was low. At operation on the right side, the right pulmonary artery was described as being "1.0 cm. in diameter and extremely flabby."

Comment: The method demonstrated that there was not a tricuspid atresia and that there were two ventricles. The pulmonary arteries were well shown and appeared suitable for anastomosis.

CASE VI: TETRALOGY OF FALLOT; HIGH DEGREE OF PULMONIC STENOSIS: P. D., a white boy of ten years, had been cyanotic since birth. He was severely incapacitated and squatted frequently.

Physical examination showed marked cyanosis, with clubbing of the fingers and toes. The heart action was regular and the heart sounds were described as normal. The usual murmur of pulmonic stenosis was absent. The electrocardiogram showed a right axis deviation but no evidence of the usual right ventricular hypertrophy. Fluoroscopy showed that the heart was not enlarged and had a normal contour. A conventional film (Fig. 7A)

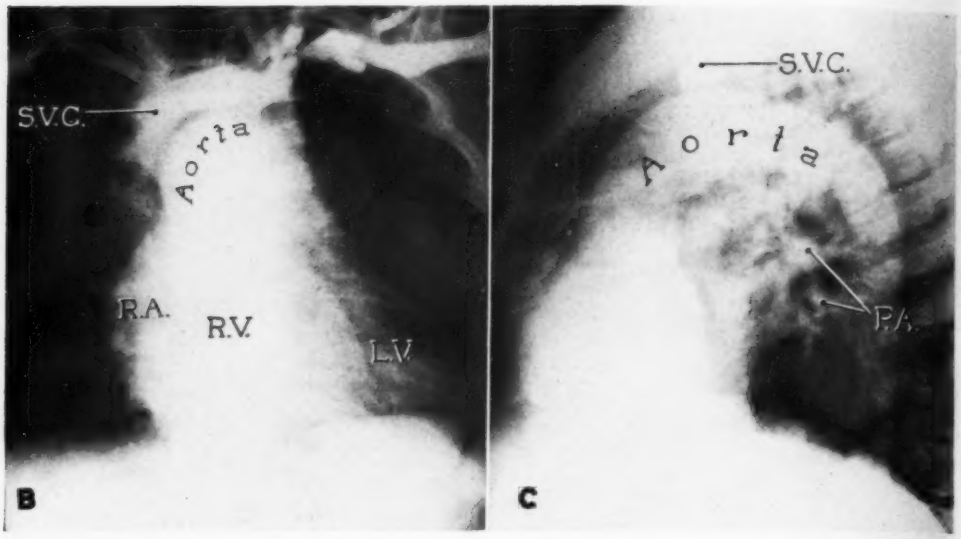

Fig. 7, B and C. Case VI. B. Film made three seconds following injection. The superior vena cava, right ventricle, and aorta are visualized. There is no evidence of a pulmonary trunk or pulmonary arteries. C. Film made three seconds after injection in right lateral projection. No evidence of a pulmonic trunk. Hilar vessels are faintly outlined, with some radiating strands representing pulmonary arterial branches.

confirms these findings. There is no evident concavity in the region of the pulmonic trunk. It was thought that the patient had a tetralogy but that there was some complicating factor.

Angiocardiography: A film made three seconds after injection in the anteroposterior projection (Fig. 7B) shows no evidence of a pulmonary trunk or pulmonary arteries. Films made at intervals of one second before and after this film likewise failed to reveal any pulmonary trunk. In the lateral view, at the same time (Fig. 7C), one sees opacities in the hilar region as well as some poorly defined vessels probably representing pulmonary arteries. The right auricle, right ventricle, and overriding aorta are readily seen. The patient was obese and had a relative increase in the anteroposterior dimensions of his chest. The findings were thought to be suggestive of pulmonary atresia with pulmonary arteries filling by collaterals. It was admitted that this could not be said with certainty.

At operation on the right side, a small pulmonary artery entirely lacking in pulsations was found. It was sufficient in size to permit an end-to-end anastomosis with the right subclavian artery. Many collateral vessels were found to be present in the mediastinum.

Comment: By angiocardiogram it was not possible to differentiate between a severe stenosis and an atresia. Before operation, the presence of a right pulmonary artery could not be diagnosed with certainty. Failure to demonstrate pulmonary trunks by angiocardiography does not necessarily preclude the possibility of successful surgical therapy.

CASE VII: TETRALOGY OF FALLOT; HIGH DEGREE OF PULMONIC STENOSIS: D. L., a white boy of four and a half years, had been cyanotic since shortly after birth. Activity had always been limited, and at the time of admission he could walk only one block very slowly.

Physical examination showed moderate cyanosis and clubbing of the fingers and toes. There was no thrill and the typical systolic murmur of pulmonic stenosis was absent. A soft to-and-fro murmur best heard on expiration and audible over the base of the heart and posteriorly was noted.

Fluoroscopy and conventional roentgenography revealed a configuration typical of tetralogy of Fallot and there was a striking lack of vascular pattern in the lungs. There was doubt as to the presence of a right pulmonary artery.

Angiocardiography: A film made at the end of three seconds (Fig. 8A) in the anteroposterior projection demonstrates a right superior vena cava, the right auricle, and overriding aorta. There is no evidence of a pulmonary trunk. In the hilum of the left lung is a vessel which does not appear to contain much of the contrast solution. A film made two seconds later (Fig. 8B) shows a slight but definite increase in density of this vessel, and several small vessels are noted in the right lung. The sequence suggests that these vessels filled later than

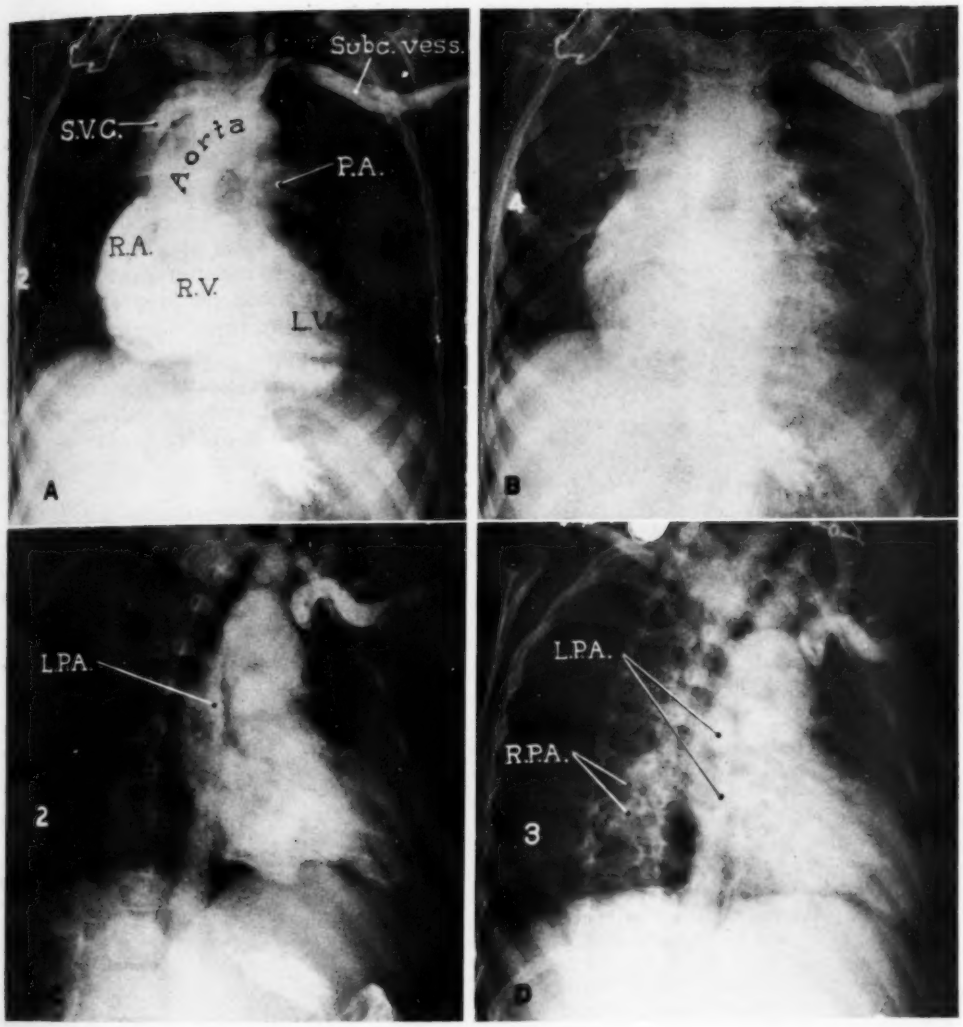

Fig. 8. Case VII. A. Roentgenogram made three seconds after injection. Vessel in hilum of left lung is visualized but apparently contains little of the contrast solution. Right auricle and overriding aorta are clearly visualized. Interventricular septum is obscured by presence of contrast solution in both right and left ventricles. The pulmonary trunk is not seen.

B. Film made two seconds following A. Contrast solution is now seen in smaller branches of the pulmonary artery in both lungs.

C. Film made in left posterior oblique position three seconds after injection. There is a rounded area of increased density in the hilum of the lung which is thought to represent the pulmonary artery.

D. Film obtained one second following C. The vessel previously noted is more readily apparent, and small vessels are seen in both lung fields.

usual, since the distal aorta fills quite well before the pulmonary arteries are visualized. In a film made in the left posterior oblique position at three seconds (Fig. 8C), there is no direct evidence of a vessel in the right hilum. A film made one second later (Fig. 8D) demonstrates the right pulmonary arteries seen end-on, and numerous small branches coursing through the lung fields. In retrospect one may see the early opacification of this vessel in Fig. 8C. We reported the presence of a small right pulmonary artery.

At operation the right pulmonary artery was described as "rather small." It was identified without great difficulty.

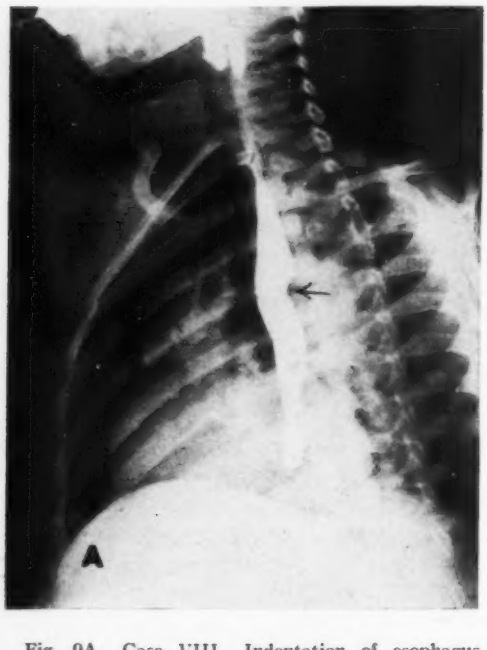

Fig. 9A. Case VIII. Indentation of esophagus (arrow) by retro-esophageal vessel. This defect was noted in all positions at fluoroscopy.

Comment: The difficulty of distinguishing a severe stenosis from an atresia is again demonstrated. The pulmonary artery may be small and fill so slowly that it is not definitely visible until several seconds after the aorta has filled. If the pulmonary artery is visualized by angiocardiography, however, the route by which it fills is of less significance than its size and position, since a successful anastomosis may be done with a vessel of adequate size even if the portion near the heart be completely occluded. It should be noted, however, that a pulmonary artery which fills by collateral vessels only is likely to be extremely small and therefore less apt to permit the performance of a successful anastomosis.

"*Pseudo-Truncus Arteriosus*"

CASE VIII: FUNCTIONAL TRUNCUS ARTERIOSUS: S. S., a white girl of twenty-six months, was cyanotic at birth. Her activity was severely limited, and on entry she could walk only one block slowly.

The child was intensely cyanotic. There was a loud continuous murmur over the right chest anteriorly and posteriorly.

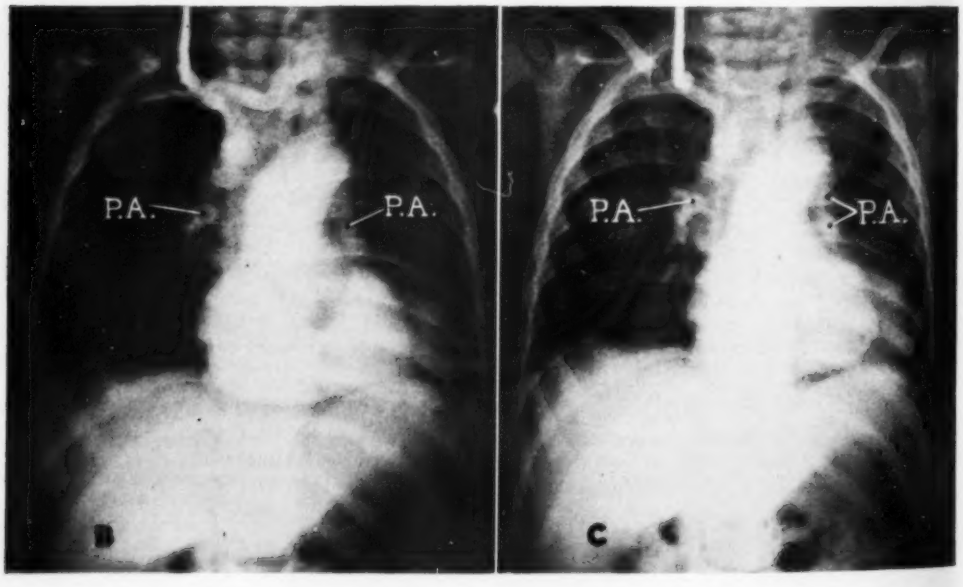

Fig. 9, B and C. Case VIII. B. Film made three seconds after injection. No evidence of a pulmonary trunk is seen, although an opacity is present in both hilar regions. C. Film made one second after B. The hilar opacities are more pronounced, and spidery branches are seen on the right.

Fluoroscopy and conventional roentgenography showed that the heart was not enlarged. The vascular shadows on the right were more prominent than on the left. A constant indentation (Fig. 9A) in the posterior wall of the esophagus was thought to represent a retro-esophageal vessel. The patient was referred for angiocardiography for the purpose of determining whether or not pulmonary arteries were present.

Angiocardiography: A film made three seconds after injection (Fig. 9B) in the anteroposterior projection shows the right auricle, the right ventricle, and the overriding aorta. There is no evidence of a pulmonic trunk, although in the film made one second later (Fig. 9C) there is increased opacity in the spidery vessels at the hilum of the right lung, as well as some increased density in the hilum of the left lung. Small pulmonary arteries were thought to be present.

At operation, the right pulmonary artery was found with difficulty, due to its small size. It could not be identified with certainty since its bifurcation was connected to the heart only by a fibrous strand. A large systemic vessel arose from the aorta on the left side, coursed posterior to the esophagus and right bronchus, and entered the hilum of the right lung. It was undoubtedly responsible for the posterior indentation in the esophagogram. An anastomosis between the right subclavian and the bifurcation of the right pulmonary artery was started, but in the midst of the procedure the heart stopped and the patient could not be revived. At autopsy no evidence of a left pulmonary artery or of a pulmonic trunk could be found. All of the blood supply to both lungs came from the bronchials, the large retro-esophageal vessel mentioned above, and other small arteries arising from the aorta.

Comment: A vessel in the hilum of the right lung was demonstrated, but it could not be told with certainty whether it was a pulmonary artery or a systemic vessel. It filled slightly later than the pulmonary artery was expected to fill and, in retrospect, it was higher in the mediastinum than normal. A pulmonic trunk was not demonstrated. It will be noted that even though there was pulmonary atresia and the main pulmonary artery was represented by a fibrous cord, the distal portion of the pulmonary artery on the right was present and large enough for an anastomosis. Had this been completed, there is every reason to believe that the patient would have been benefited.

Fig. 10A. Case IX. Conventional roentgenogram showing concavity of left border of the heart. The vascular markings are inconspicuous.

CASE IX: "PSEUDO-TRUNCUS ARTERIOSUS": A. P., a seven-year-old white girl, was noticed to be cyanotic at the age of six months. The cyanosis became progressively more evident, especially during the year before hospital admission. The patient's activity had always been limited and she could walk less than a block before stopping.

Physical examination showed moderate clubbing of the fingers and toes and well marked cyanosis. The heart sounds were of good quality and the heart action was regular. During inspiration, a high-pitched systolic murmur was heard in the pulmonic area and in the left interscapular area posteriorly. This murmur disappeared with expiration.

Conventional roentgenography (Fig. 10A) reveals a cardiac configuration typical of a tetralogy of Fallot. The lungs show diminished vascular markings. Clinically the patient was thought to be a good candidate for surgery and angiocardiography was not carried out.

At operation on the right side, only thread-like strands of tissue representing the pulmonary artery could be found. At least one good-sized systemic artery could be seen entering the hilum of the right lung. The subclavian artery on the right side was retro-esophageal and arose from the descending aorta. No anastomosis could be performed.

Angiocardiography: Angiocardiography was performed on the eleventh day after operation. A film

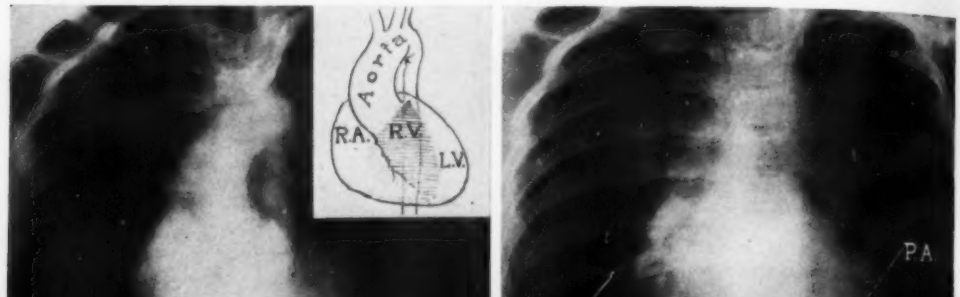

Fig. 10, B and C. Case IX. B. Roentgenogram made two seconds after injection. Right ventricle ends in a pointed projection and no pulmonary trunk is seen beyond it. C. Roentgenogram made at six seconds. Fine feathery markings in the lungs are shown. These represent pulmonary arteries filling through collaterals.

made two seconds after injection (Fig. 10B) is strikingly similar to those in Case VIII. The right auricle, right ventricle, and overriding aorta are outlined. There is no evidence of a pulmonary trunk or pulmonary arteries and the lung fields show decreased vascular markings. A film made six seconds after injection (Fig. 10C) shows fine feathery markings scattered diffusely through the lung parenchyma. This was interpreted as being due to contrast solution which had reached the lungs through collateral circulation.

Comment: Pulmonary atresia is compatible with a life span of several years. This condition can be strongly suspected from angiocardiographic findings. As indicated previously, we use the term "pseudo-truncus arteriosus" for that group of patients in which the main circulation to the lungs is through collateral arteries arising from the aorta. There is atresia of the pulmonic outlet which may be combined with obliteration of portions of the pulmonary artery. The distal portions of the artery may persist and can be filled through collateral channels.

DISCUSSION

It should be emphasized that no single diagnostic test will provide complete understanding of the anatomical and physiological abnormalities in a patient with congenital cyanotic heart disease. Many cases may be diagnosed with considerable accuracy on the basis of the history, physical examination, and conventional roentgenography, with emphasis on fluoroscopy. Study of the blood, including gas analysis, yields additional helpful information, while the more complex physiological tests, including catheterization of the heart chambers, are often invaluable.

Angiocardiography is an additional valuable weapon in this armamentarium, but for full realization of its value one should employ it, whenever possible, in conjunction with the studies noted above. Even then it may present certain technical deficiencies or be subject to the misinterpretations common to all radiographic technics. It is unfortunately true that after all of the studies enumerated above, a congenitally cyanotic patient may come to surgery with his basic difficulty only incompletely elucidated. Even after surgery the picture may be confusing and only with autopsy examination will this confusion be resolved.

A continued effort to correlate the results of all diagnostic procedures and to evaluate their validity by operative or pathologic

study will lead to greater accuracy in interpretation of all tests including angiocardiography.

SUMMARY

With the advent of surgical therapy for congenital heart disease of the cyanotic type, the necessity for exact diagnosis has become more important.

Angiocardiography is a valuable technic in establishing an accurate diagnosis, when employed in conjunction with clinical, laboratory, and physiological studies, such as catheterization of the heart.

The authors have used this technic in 75 patients with congenital cyanotic heart disease; 140 injections have been made without serious reaction.

Nine patients have been selected for detailed consideration in order to emphasize the advantages and shortcomings of the method in preoperative evaluation.

Seven patients had the tetralogy of Fallot and two had a truncus arteriosus. All were subjected to operation, and in one instance postmortem studies were available.

An overriding aorta could be demonstrated in all instances, as well as the position of the descending aorta.

An interventricular septal defect may sometimes be directly demonstrated.

Direct visualization of the pulmonary conus is so difficult as to be untrustworthy, but strong presumptive evidence of stenosis may often be obtained. It is not possible by angiocardiography alone to distinguish pulmonary atresia from a high degree of stenosis.

The presence and character of the pulmonary arteries may be reliably determined. Failure to demonstrate the proximal portions of the pulmonary artery, however, does not rule out the possibility of a successful anastomosis.

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SUMARIO

La Angiocardiografía en la Cardiopatía Congénita de Forma Cianótica con Estenosis o Atresia Arteriopulmonar

Con el advenimiento de la terapéutica quirúrgica en la cardiopatía congénita de tipo cianótico, la necesidad del diagnóstico exacto ha cobrado mayor importancia. La angiocardiografía representa una técnica valiosa para establecer dicho diagnóstico, si se emplea junto con los métodos de laboratorio, clínicos y fisiológicos, tales como el cateterismo cardíaco. Los AA. han utilizado esta técnica en 75 enfermos de dicho género, habiendo ejecutado 140 inyecciones sin observar reacciones graves. A fin de recalcar las ventajas y deficiencias del método en la justipreciación preoperatoria, nueve enfermos del grupo han sido escogidos para estudio pormenorizado.

Siete pacientes mostraban la tetralogía de Fallot, y dos, tronco arterioso. Todos fueron operados, y en un caso se cuenta con estudios autópsicos. En todos pudo observarse la sobreposición de la aorta así como la posición de la aorta descendente. A veces puede notarse directamente la existencia de un vicio del tabique interventricular.

Es tan difícil la visualización directa del cono pulmonar que no puede confiarse en ella, pero pueden obtenerse a menudo poderosos datos presuntivos de estenosis. Con la angiocardiografía por sí sola, no es posible diferenciar la atresia pulmonar de una estenosis pronunciada.

La presencia y naturaleza de las arterias pulmonares pueden ser determinadas con seguridad. Sin embargo, la inobservación de las porciones proximales de la arteria pulmonar no excluye la posibilidad de una anastomosis feliz.

Aid of Arteriograms in Diagnosis and Treatment of Intracranial Aneurysms[1]

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THE PROBLEM OF diagnosis and treatment of intracranial aneurysms falls heavily on the shoulders of the radiologist and neurosurgeon since the introduction of arteriograms by Egas Moniz, who showed the visualization of the intracranial arterial and venous systems to be a practical procedure to determine not only the presence of aneurysms but also any variation in the blood vessels (size, shape, and position).

There should be a healthy co-operation between the personnel of the departments of radiology and neurosurgery. If that co-operation is not absolute, adequate arteriograms, which are imperative for establishing the diagnosis and arriving at a logical program in the treatment of the aneurysm, cannot be uniformly obtained. It is the duty of the roentgenologist to be well informed regarding the normal and anomalous anatomy of the circle of Willis and its branches. It is not enough to determine whether an aneurysm is present; he must also attempt to perfect himself in accurate descriptions of the exact relationship of the aneurysm to the openings or stomas of the larger branches of the circle of Willis. His ability to do so accurately will lighten some of the surgeon's burden of decision in the treatment of the aneurysm. Any surgeon who has attempted to treat patients with intracranial aneurysms realizes, if he is intellectually honest, that he needs all the information and help possible regarding the aneurysm before he actually institutes treatment. I realize that this may be the attitude of a pessimist; however, carefully worked out information is frequently rewarded by a brilliant result, whereas a decision hastily made without adequate information may end in a major catastrophe. For this reason, I cannot lay too great stress upon this co-operation. When the information concerning an aneurysm is obtained, it must not result in dilatory tactics and decisions, while the patient is allowed to die from the underlying condition.

In a series of 114 intracranial aneurysms in 110 cases studied by the writer, the etiology presumably was related to congenital defects in the arterial wall. One exception was a patient with mycotic emboli. Hypertension was noted in 23 cases. In none was syphilis a factor. It is of interest that in 63 cases the aneurysm was found on the left side and in 47 on the right. Seventy-two patients were females and 38 were males. The majority of symptoms occurred in patients between the ages of twenty and sixty; the youngest patient was fourteen and the oldest seventy.

Unfortunately, there is no clinical syndrome that makes the diagnosis of an unruptured intracranial aneurysm a reasonable certainty, without evidence of subarachnoid hemorrhage. There are certain symptoms, however, which arouse suspicion of its presence. The symptoms in the 110 cases were as follows: generalized headache in 45; unilateral headache in 47; headache of migrainous type in 4; facial pain in 8; convulsions in 11; vertigo and dizziness in 11; signs of hypopituitarism in 4. Eighty-two patients had subarachnoid hemorrhage as the initial symptom, and 52 had cranial nerve changes (involving the second, third, fifth, or sixth nerve).

The diagnosis of intracranial aneurysm should be made, if at all possible, before rupture, because of the serious results attendant upon that complication. Approximately 35 per cent of patients die with the

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

Fig. 1. Subclinoidal calcified aneurysm of the internal carotid artery

first rupture and 21 per cent die in recurrent attacks. Since many of the recurrent hemorrhages take place within three weeks of the initial hemorrhage, it is important that an attempt be made to establish the diagnosis as well as to determine whether the aneurysm is located at a site that is amenable to surgical intervention or whether the patient's chances are equally favorable without an operation.

It is significant that in our surgical series of 110 patients with intracranial aneurysms, only 9 were encountered in a period of ten years, while 101 were found in the past four years, chiefly because of an awareness that such a condition might be present. Because of this suspicion, diagnostic aids were utilized either to prove or to disprove the presence of an aneurysm. From the standpoint of treatment the importance of verification of the diagnosis, so that one can advise the patient and family intelligently, cannot be overemphasized. There can be no question that to institute treatment the physician must first know whether the patient actually has an aneurysm; he must know the exact site of the aneurysm and its relation to the other large vessels of the circle of Willis or its branches; he must know the tolerance of the affected hemisphere to reduction in blood supply, that is, the efficiency of the collateral circulation; he must know the risk involved in non-surgical intervention *versus* that of the direct or indirect surgical attack; he must know the time a secondary hemorrhage is likely to occur; he must utilize every test and laboratory facility possible to gather all the information he can about the aneurysm before definitely committing himself as to the proper course of treatment.

The temporary occlusion of the internal carotid artery by digital compression will give valuable information regarding the tolerance of the affected hemisphere to the partial ischemia and the collateral circulation. One must be cautious, if subjective symptoms occur, in assuming that they are from actual ischemia rather than from indirect ischemia as a result of an irritable carotid sinus. This can readily be determined either by massaging the carotid sinus or by occluding the common carotid artery well below the bifurcation.

Roentgenograms of the skull may be of great value in the larger aneurysms which have enlarged the sella turcica unilaterally, elevated one of the anterior clinoids or perhaps sharpened the latter by pressure from below. The thinning of the lateral margin of the optic foramen, as described by Jefferson, may also be of aid in the differential diagnosis. Only the large aneurysms in direct contact with bone can possibly cause changes, with the exception of possible calcification which may occur in an aneurysm (Fig. 1). Sosman has described the fine crescentic outlines or dense calcifications that may be found. The final diagnosis, therefore, rests on either the arteriogram or direct surgical exploration. In my experience arteriography has been of great help, allowing one to study the relationship of the aneurysm to the main branches of the circle of Willis. For this reason, arteriograms are now made on all patients suspected of having an aneurysm. Well over 200 arteriograms have been completed, in

most instances with thorotrast. More recently, however, diodrast, has been employed with no untoward results. Before diodrast is used, all patients are tested for sensitivity to iodine.

I have no hesitation in injecting thorotrast or diodrast at any time in the presence of a recent subarachnoid hemorrhage if an 18-gauge needle is used, since any increased intra-arterial pressure due to the injection is dissipated before the site of the aneurysm is reached. Many times it is impossible to determine from the physical examination or the history the side on which the aneurysm is located. Therefore, both carotid arteries and their branches should be visualized by the closed method, so that the proper site of the leaking aneurysm may be determined before surgical interference is instituted. Since 75 per cent of intracranial aneurysms involve the anterior two-thirds of the circle of Willis, one should begin the investigation by visualization of that portion of the cerebral circulation. The posterior third of the intracranial circulation can be demonstrated only by the closed method whenever the patient has a high subclavian artery. I have seen the vertebral arterial system filled in patients with thrombosis of the internal carotid artery at the bifurcation in the cervical region. It is conceivably possible, therefore, to visualize the system in this manner if the external and internal arteries are temporarily occluded during injection of the common carotid.

The method of injection is important. At present I use only the closed method, since it may be employed in patients with equivocal signs of aneurysm and in whom air studies have proved normal. The arteriograms can be made with the patient still asleep from the pentothal anesthesia, immediately following the review of the encephalogram. I do not use the open method routinely because one is inclined to ligate the internal carotid artery in the neck as soon as the aneurysm can be seen on the wet x-ray film. Adequate study may not be made of the exact site of the aneurysm. If a direct attack of the aneurysm seems indicated, as much blood supply as possible should be retained. In such cases ligation in the neck should be left undone.

Fig. 2. Position of patient and relationship to upright automatic plate changer.

In patients with headaches of undetermined origin with normal air studies, vascular changes have not been excluded. For this reason the indirect or so-called closed method of arteriography is only an added minor procedure, whereas exposure of both carotid arteries verges on the major, nor is one assured of better filling with the open than with the closed method. I am not at all certain that the practice of exposure of the common carotid artery or internal carotid artery for the purpose of making arteriograms may not be more hazardous than the closed method if the external carotid and common carotid arteries are occluded at the time of injection. The distention of the internal artery and its branches with thorotrast or diodrast, when it cannot be carried quickly into the venous return, may well cause changes which would not take place if the solution were injected directly into a normal flowing blood stream.

It is important to keep in mind that the completion of a satisfactory arteriogram is dependent upon the teamwork of the operator, the x-ray technician and, of course, the physical equipment, namely the x-ray apparatus and the syringe and needle, which must be in perfect working order. The patient is allowed to remain on the carrier stretcher on which he has been

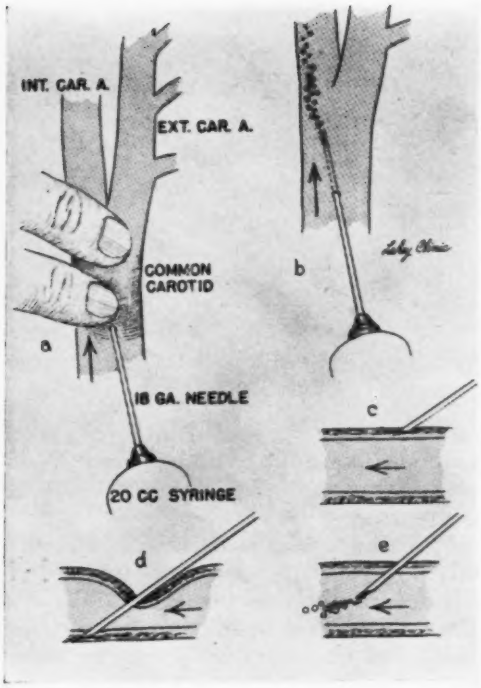

Fig. 3. Principle of stream-line flow. The needle must be directed toward the internal carotid artery.

transported to the x-ray department. The wheels of the carriage are fixed so that no motion can take place at the time of injection. With the patient on his back, a pillow or folded blanket is placed under the shoulder blades and two turkish bath towels are placed under the occiput (Fig. 2). Care must be exercised to prevent overextension of the patient's neck either by lifting up the chin during the pentothal anesthesia or by allowing the head to rest considerably lower than the chest, since this narrows the lumen of the artery and may in some instances occlude it by the stretch over the tubercle of the sixth cervical vertebra. The patient's head is allowed to remain in a horizontal position, and an 18-gauge needle, 2 inches long, with a very sharp point and moderately curved bevel, attached to a 20-c.c. Luer-Lok syringe by a two-way petcock, is directed so that the point of the needle engages the adventitia of the common carotid artery approximately 1 to 2 cm. beneath the bifurcation. As soon as the needle is firmly engaged in the lumen of the artery, arterial blood can be seen pulsating into the citrate solution in the attached syringe. One must be certain that the needle is well engaged in the lumen of the artery and will not be displaced by the injection. It is well to make several practice injections with the citrate solution used to prevent clotting of the blood in the syringe and needle.

Fig. 4. Specimen of a large ruptured aneurysm involving the entire right anterior half of the circle of Willis, precluding successful intracranial extirpation.

If several cubic centimeters can be injected rapidly and a free back-flow of arterial blood takes place immediately, with the needle directed toward the lateral wall of the common carotid artery, the syringe with the diodrast is then attached and the solution injected as rapidly as permitted through the 18-gauge needle. Great care must be exercised to prevent the injection into the carotid system of bubbles of air which become caught in the hub of the needle as the syringe is attached. Certain

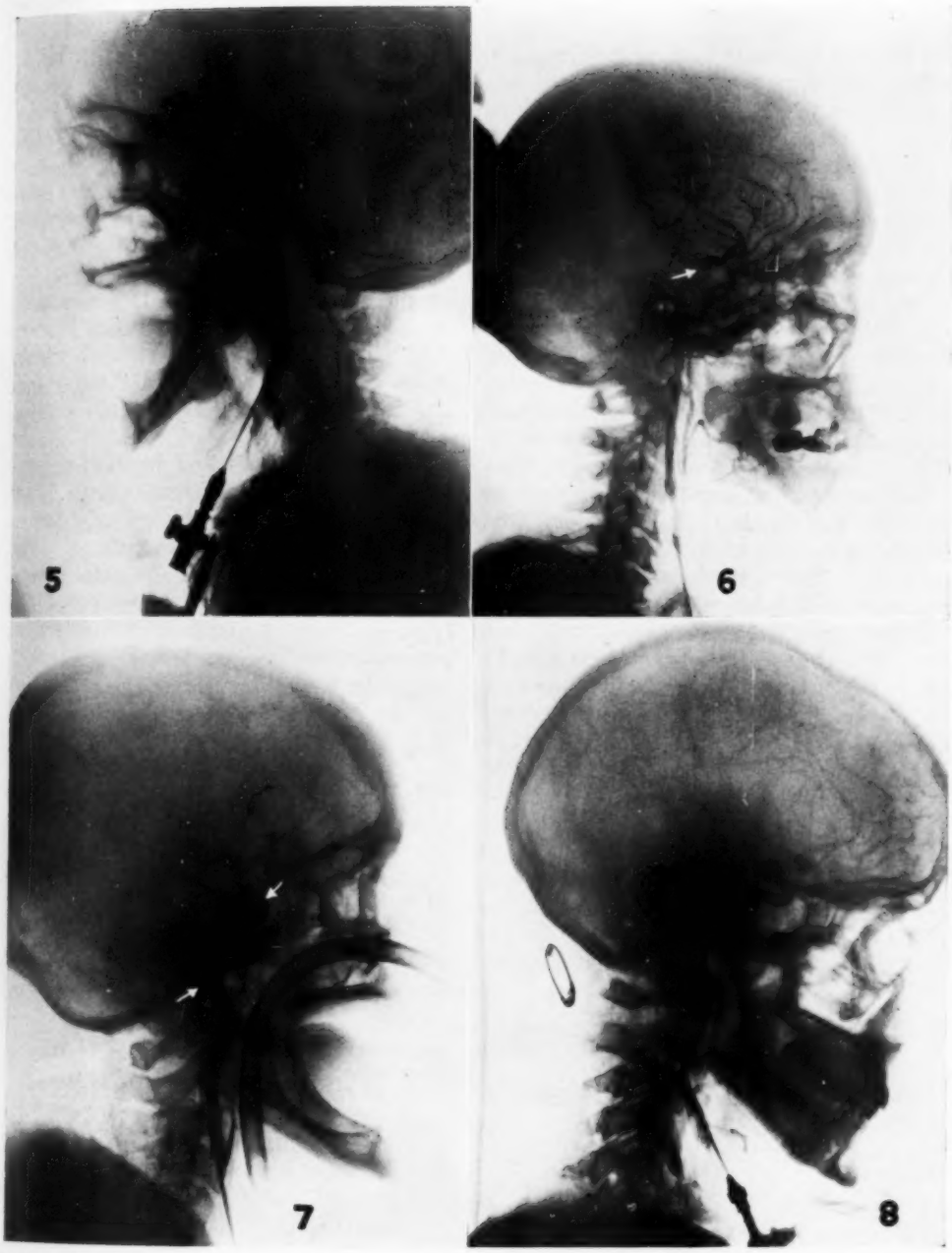

Fig. 5. Arteriogram of a large saccular aneurysm involving the internal carotid, anterior cerebral, middle cerebral, anterior choroidal, and posterior communicating arteries.

Fig. 6. Arteriogram demonstrating aneurysm of a vestigial vessel, so-called "nubbin."

Fig. 7. Arteriogram demonstrating aneurysm favorable for trapping.

Fig. 8. Arteriogram demonstrating saccular aneurysm of the internal carotid and a second involving the anterior cerebral artery.

serious sequelae can take place from air emboli and may account for some of the convulsions which have been reported to occur during injection. The contrast medium should be injected toward the lateral lumen of the common carotid artery because a definite law of stream-line flow holds true in the arterial system (Fig. 3). In other words, the contrast medium, if injected laterally and downward, will follow the blood stream into the internal carotid artery, whereas, if the contrast medium is injected medially and upward, most of it will appear in the external carotid artery. It is necessary that the x-ray technician be made aware that the injection is about to start. The x-ray tube is prepared for making the exposure. The head is thoroughly aligned with the upright automatic Bucky, suitable for stereoscopic exposures, which is used routinely for chest roentgenograms; 20 c.c. of the diodrast has been placed in the 20-c.c. syringe and 15 c.c. is injected rapidly, and the first exposure is made. The injection is continued during the automatic shifting of the x-ray tube, and the films are taken for the second exposure. This allows adequate filling for stereoscopic films; in most instances the latter are more satisfactory than a single lateral and a single anteroposterior view.

The operator and assistant must be careful not to allow themselves to be exposed to x-rays beyond the dosage that is safe for their own welfare. The dosage that can be tolerated may be readily computed by the roentgenologist, and one should abide by his judgment.

Many intracranial aneurysms are favorably situated for excision or intracranial trapping; others are located so that direct attack would almost certainly invite disaster (Figs. 4–8). These latter should be treated by the indirect method of ligation of the internal carotid artery in the neck, or in some instances remain untreated. Multiple aneurysms have been found at autopsy in 10 per cent of cases. This fact can be determined before death of the patient only by the use of arteriograms. From the facts presented in this paper, one can readily understand the importance of the radiologist in both the diagnosis and treatment of intracranial aneurysms.

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SUMARIO

Ayuda Prestada por los Arteriogramas en el Diagnóstico y el Tratamiento de los Aneurismas Intracraneales

La cooperación entre el radiólogo y el neurocirujano es indispensable para el diagnóstico y tratamiento de los aneurismas intracraneales, pues los arteriogramas adecuados son de rigor para establecer el diagnóstico y determinar el tratamiento.

Las radiografías del cráneo puden ser de valor diagnóstico, por mostrar la hipertrofia de la silla turca, la elevación de una de las clinoides anteriores y posiblemente la agudización de la última por la presión desde abajo; pero sólo los aneurismas más grandes producirán tal patología. El diagnóstico definitivo corresponde, pues, al arteriograma o a la exploración quirúrgica. El A. emplea la arteriografía sistemáticamente, por permitir el estudio de la relación del aneurisma con las principales ramas del círculo de Willis, utilizando el torotrasto, y más recientemente, el diodrasto (previas pruebas de la sensibilidad), con un sistema cerrado. Visto que 75 por ciento de los aneurismas intracraneales afectan las dos terceras partes anteriores del círculo de Willis, la investigación comienza con dicha porción de la circulación cerebral. La técnica va descrita.

The Angiocardiographic Measurement of the Normal Great Vessels[1]

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SINCE THE EARLY roentgenographic era, many methods have been employed to estimate the size of body structures by the measurement of their roentgen images. In cardiac roentgenography, distortion has been reduced to a minimum through the use of teleroentgenography. A comprehensive review of roentgenographic measurement of the heart has recently been made by Ungerleider (1).

Measurement of the diameter of the aorta has been a controversial subject, and methods for its accomplishment have been many. All projections have been employed to delineate the ascending, transverse, and descending aorta. The width of the superior mediastinum in the frontal projection affords a poor estimate of the aortic diameter, as it may be widely altered by arteriosclerotic tortuosity or hypertensive unfolding of the aorta. The best aortic measurement in the frontal projection, that between the outermost point of the aortic knob and the barium-filled esophagus, is subject to variation in the thickness of the esophageal wall and of the tissues between it and the aorta. The method gives no impression of the thickness of the aortic wall. The customary left anterior oblique measurement, though occasionally satisfactory in the presence of arteriosclerotic or syphilitic calcification of the aorta, is generally misleading because of the difficulty in outlining the inner or inferior margin of the aorta (2).

Many methods of determining the degree of enlargement of the pulmonary arterial tree suffer from the fact that the measurements are indirect (3). Standards have varied widely with the method used, and interpretation of figures has been difficult.

The roentgen diagnosis of syphilitic aortitis has depended largely upon the intimal deposition of calcium in the aorta, often a late manifestation. The aorta in its ascending portion is indistinguishable from the cardiac shadow, and thus that portion of the vessel earliest affected in syphilitic disease is not demonstrated by conventional methods. Early pulmonary heart disease is not detected because of the failure of the conventional roentgenogram to afford accurate measurements of the pulmonary artery.

With the advent of a practical method of angiocardiography in 1938 (4), measurements of the great vessels have become simple and reliable, and comparable results are obtained by independent observers. Not only may the caliber of the aorta and pulmonary artery, as well as of their branches, be measured, but often the thickness of the vessel wall may be clearly demonstrated.

THE AORTA

One hundred normal aortas visualized angiocardiographically have been analyzed. The various projections were employed and were found to check within one or two millimeters of each other in a given case. Presumably, variations were based on the different distances between aorta and film in different projections, since the aorta is round in normal subjects. The most satisfactory projection was found to be the left anterior oblique, which reveals the entire intrathoracic aorta. The end-on aortic arch as seen in the right anterior oblique and frontal projections does not lend itself to satisfactory measurement because of superimposition of ascending and descend-

[1] From the Department of Radiology of The New York Hospital-Cornell Medical Center. This investigation was aided by a grant from the Schering Corporation, manufacturers of Neo-Iopax (75 per cent). Accepted for publication in February 1948.

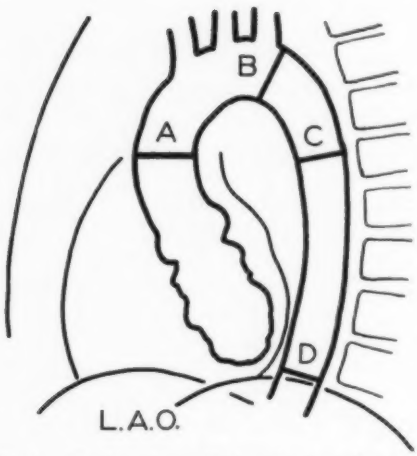

Fig. 1. Tracing of opacified aorta in left anterior oblique projection. Sites of measurement: (A) mid-ascending, (B) transverse, (C) descending, (D) diaphragmatic.

ing portions of the arch. The four aortic measurements (ideally visualized in the left anterior oblique projection) utilized in this study are shown in Figure 1.

(A) *Mid-ascending:* The diameter of the column of contrast substance is measured at the mid point of the ascending portion of the arch, a hitherto unmeasurable region of considerable importance in many pathological conditions of the aorta.

(B) *Transverse:* Measurement is made at the junction of the left side of the left subclavian artery and the aortic arch. This measurement gives the internal diameter of the arch distal to the origin of its major brachiocephalic branches, and is also important in that this site is often affected by congenital variations in aortic caliber, such as coarctation of the aorta and patent ductus arteriosus.

(C) *Descending:* Measurement is made on the same plane as is used in measuring the ascending aortic arch, a convenient point of reference.

(D) *Diaphragmatic:* The aorta is measured as it traverses the diaphragm, a constant anatomic point.

Results are summarized in Table I. The ascending aorta was found to vary between 16 and 38 mm., averaging 28.6 mm. in 100 patients with normal aortas. The age range in these patients was from five to sixty-five years, with an average of 35.3 years. The transverse aorta distal to the point of origin of the brachiocephalic arteries was considerably smaller, ranging from 13 to 34 mm., averaging 24.8 mm. in 44 cases. The descending aorta, measured in 58 cases, varied between 12 and 32 mm., with an average of 22.9 mm. At the point of passage through the diaphragm, in 54 cases the aortic caliber ranged from 9 to 28 mm., averaging 19.7 mm.

In arriving at the above figures, the frontal projection was found to be of value regularly only in measurement of the ascending aorta, occasionally in measurement of the descending aorta, often of the diaphragmatic aorta, but never of the transverse arch. The right anterior oblique projection, employed in only 7 cases, was more satisfactory than the frontal projection but, being a projection of minor value in angiocardiography, was rarely used. No case was included in this series unless at least one reliable measurement of the ascending aorta could be made, regardless of the projection employed.

Comparative measurements of the ascending aorta were made in frontal, left anterior oblique, and left lateral projections. In 6 instances where frontal and left anterior oblique measurements were available on the same patients, the left

TABLE I: SUMMARY OF RESULTS IN MEASUREMENT OF 100 SELECTED NORMAL AORTAS AND 50 SELECTED NORMAL CENTRAL PULMONARY ARTERIAL BEDS ANGIOCARDIOGRAPHICALLY VISUALIZED

AORTA	CASES	RANGE, MMS.	AVERAGE, MMS.
A ASCENDING	100	16–38	28.6
B TRANSVERSE	44	13–34	24.8
C DESCENDING	58	12–32	22.9
D DIAPHRAGM	54	9–28	19.7
PULM. ART.			
A CONUS	10	16–24	19.1
B MAINSTEM	22	20–30	26.4
C RT BRANCH	50	17–30	23.4

anterior oblique measurement averaged 1.3 mm. higher than the frontal measurement. In 6 cases measured in both frontal and left lateral projections, the lateral measurement averaged 1.7 mm. higher than the frontal. The average caliber of the ascending aorta in 57 cases measured in frontal projection was 28.2 mm., while in 36 cases measured in left anterior oblique projection, the average was 29.2 mm., and in 15 cases measured in left lateral projection, the average was 30.2 mm. Left anterior oblique and left lateral measurements of the ascending aorta thus tend to be slightly

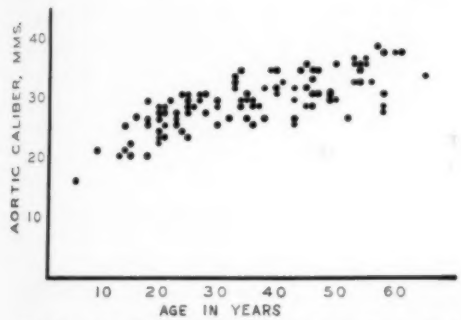

Fig. 2. Age-caliber relationship in measurement of ascending aorta in 100 selected normal aortas visualized angiocardiographically. Note increasing caliber of aorta with advance in age.

greater (1–2 mm.) than the corresponding frontal measurement, a fact partly accounted for by the variation in distance between the aorta and film in the different projections. The effect of this slight variation was disregarded in arriving at normal range and average measurements set forth in this study.

It was frequently found possible to measure the thickness of the aortic and pulmonary artery walls, which varied between 1.5 and 2.5 mm. Occasionally, with angiocardiography, an arteriosclerotic plaque may be accurately localized.

In selecting cases for measurement, only those without clinical or roentgenographic evidence of aortic abnormality were used, with the single exception of atherosclerosis, a condition so often present roentgenographically as to necessitate its inclusion. It is extremely difficult to rule out the

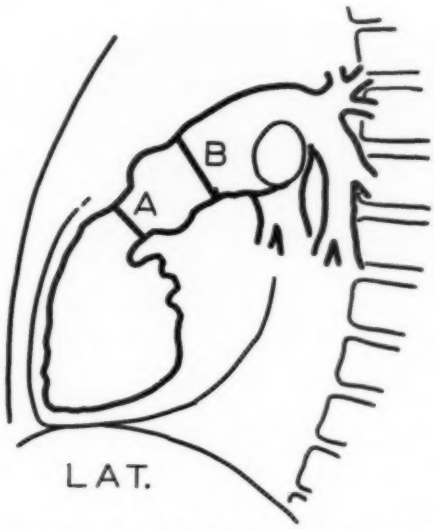

Fig. 3. Tracing of right heart and central pulmonary arterial bed opacified in left lateral projection. Sites of measurement: (A) pulmonary conus, (B) main-stem pulmonary artery.

presence of early atheromatous changes in the living person. The principal causes of dilatation of the aorta in cases excluded from this series were (1) syphilitic aortitis, (2) hypertension, and (3) aortic insufficiency, regardless of its cause. These conditions warrant individual consideration and are not discussed here.

There appears to be a direct relationship between the caliber of the aorta and the age of the patient (Fig. 2), a fact in agreement with the pathological findings (5). Whether aging processes of a general nature or more specific factors, such as atherosclerosis, are responsible for the increase in aortic caliber with advancing years cannot be determined by this study.

PULMONARY ARTERY

In 50 cases, the normal right main branch of the pulmonary artery could be measured. The pulmonary conus and the main-stem pulmonary artery, at their mid point, were best measured in left lateral and left anterior oblique projections (Fig. 3). Again, too few right anterior oblique studies were available for adequate evaluation. The end-on shadow of the right pul-

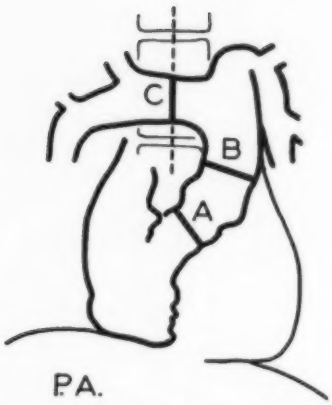

Fig. 4. Tracing of right heart and central pulmonary arterial bed opacified in frontal projection. Sites of measurement: (A) pulmonary conus, (B) main-stem pulmonary artery, (C) right branch of pulmonary artery.

monary artery, as seen in lateral or left anterior oblique projection, was not a reliable measurement, since it did not check with the more accurate frontal measurement.

The most frequent measurement was that of the right pulmonary artery, obtained in frontal projection at the body midline (Fig. 4). This measurement, made in 50 cases, varied between 17 and 30 mm. and averaged 23.4 mm. The patients ranged in age from fourteen to sixty-eight years, averaging 36.8 years. The main-stem pulmonary artery, measured in 22 cases, varied between 20 and 30 mm. and averaged 26.4 mm. in caliber. For the pulmonary conus, clearly outlined in only 10 cases, the range in caliber was from 16 to 24 mm., and the average 19.1 mm. The pulmonary conus figures, arrived at in the absence of electrocardiograph control of exposures, are probably of little significance. The left main branch of the pulmonary artery defied regular measurement, since it could not be clearly separated from the shadow of the opacified main-stem pulmonary artery.

It was noted (Fig. 5) that the age-caliber relationship present in aortic measurements is not so marked in the pulmonary artery findings, a fact which may perhaps be related to the relative infrequency of pulmonary artery atherosclerosis as compared to that of the aorta.

A large number of cases were excluded from this series because of obvious disease involving the pulmonary artery. Foremost among these pathological entities were (1) congenital heart disease, (2) chronic pulmonary disease, and (3) rheumatic valvular disease. The pathology of the pulmonary artery as seen angiocardiographically is the subject of a separate study (6).

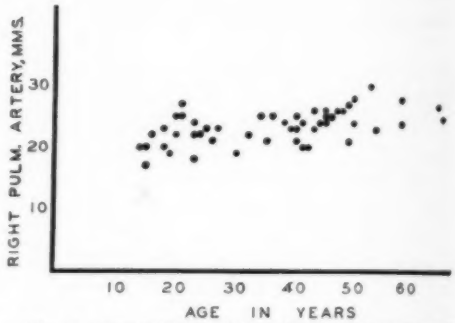

Fig. 5. Age-caliber relationship in measurement of right pulmonary artery in 50 selected normal pulmonary arteries visualized angiocardiographically.

The diameter of the right branch of the pulmonary artery as it crosses the midline of the body, seen in the frontal projection, is a simple measurement for the evaluation of the central pulmonary arterial system. Additional evidence may be obtained by measuring the caliber of the pulmonary conus and the main-stem pulmonary artery in the lateral or left anterior oblique projection.

SUPERIOR VENA CAVA

The width of the superior vena cava as it crossed the right pulmonary artery was determined in the frontal projection in 50 normal patients ranging in age from fourteen to seventy-four years. It was found to vary between 7 and 20 mm., averaging 13.0 mm. Measurements in various projections and in repeated studies on the same patient often varied as much as 6 mm. This discrepancy was probably due to venous distention by varying injection force. The upper limit of width of the

normal superior vena cava, probably about 20 mm., is often greatly exceeded in the presence of right heart failure or constrictive pericarditis.

SUMMARY

In place of conventional indirect roentgenographic measurements of great vessels, the more difficult, but far more accurate method of angiocardiographic measurement is proposed. Standard projections and points for measurement of the aorta and the pulmonary artery are presented. Results in the measurement of a selected series of cases are given. The ascending aortic caliber was found to increase in size with age, ranging between 16 and 38 mm., and averaging 28.6 mm., all ages considered. The pulmonary artery was found to be most conveniently evaluated by the measurement of the right pulmonary artery in the frontal projection. With less relation between caliber and age than in the aorta, this varied between 17 and 30 mm. and averaged 23.4 mm.

Certain objections to this method of measurement must be raised from a physiological standpoint. Until the phase of cardiac contraction is precisely controlled, measurement of cardiac and vascular structures will still be somewhat inaccurate. This is the reason why angiocardiographic measurement of cardiac wall thickness and chamber size is impractical at this time. There is already being employed a device which relates exposure to a given phase of cardiac contraction (7, 8). With this device, it is practicable to measure accurately the cardiac chambers and the great vessels in systole or diastole, and valuable information concerning cardiac dynamics is certain to be forthcoming. Normally, however, the systolic-diastolic variation in caliber of the great vessels is slight enough to make the present angiocardiographic measurements of considerable value.

CONCLUSIONS

1. Conventional roentgen measurement of the great vessels is indirect, often inaccurate, and not well standardized.

2. Angiocardiographic measurement of the great vessels is simple, accurate, and capable of standardization.

3. Methods for aortic and pulmonary artery measurement are described in detail.

4. The caliber of the ascending aortic arch gradually increases with age. It averaged in our series 28.6 mm. and ranged from 16 mm. to an upper limit of 38 mm.

5. A simple and satisfactory evaluation of the pulmonary artery may be found in measurement of the right pulmonary artery in the frontal projection. In our series, this averaged 23.4 mm. and ranged from 17 to an upper limit of 30 mm.

6. It is anticipated that larger series of angiocardiographic measurements will supplement this preliminary report.

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(For Spanish summary, see following page)

SUMARIO

La Medición Angiocardiográfica de los Grandes Vasos Normales

Debido a la inexactitud y falta de uniformidad de las mediciones radiográficas convencionales de los grandes vasos, el A. propone el empleo de la técnica angiocardiográfica, más difícil, pero mucho más exacta, presentando e ilustrando las proyecciones tipos y los puntos de medición de la aorta y la arteria pulmonar.

Ofrécese el resultado obtenido en una serie seleccionada de personas, después de excluir las que mostraban signos clínicos o roentgenológicos de afección de los vasos por medir (aparte de ateroesclerosis aórtica). El calibre de la aorta ascendente reveló aumento con la edad, variando de 16 a 38 mm. y promediando 28.6 mm., todas las edades (cinco a sesenta y cinco años) consideradas. Para valuar la arteria pulmonar, lo más conveniente resultó ser la medición de la pulmonar derecha en la proyección frontal. El calibre varió de 17 a 30 mm., promediando 23.4 mm., habiendo en este caso menos relación con la edad, que en la aorta. Las mediciones del ancho de la cava superior, al cruzar la arteria pulmonar derecha, mostraron amplia variación, siendo el límite normal máximo probablemente de unos 20 mm.

A Roentgen Finding of Unusual Interest in Perforation of the Colon[1]

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THE USUAL PATHOGNOMONIC roentgen signs of perforation of the intestine depend upon the presence of free air in the peritoneal cavity, customarily demonstrated in the erect or lateral recumbent position. Occasionally both the mucosal and serosal surfaces of an intestinal loop may be seen in the supine film when a combination of intra- and extraluminal gas is present. Successful attempts to localize the site of perforation have been few.

Certain secondary signs in the roentgenogram suggesting peritonitis are of some value. Included in this group are the demonstration of fluid in the peritoneal cavity, obliteration of the properitoneal fat, and the appearance of a generalized ileus. These latter signs, however, are in no way pathognomonic of perforation of the intestine and may be found in a variety of other conditions. For example, it is well known that the appearance of an ileus may be simulated following the administration of morphine as well as of cathartics and enemata.

In another group of cases specific evidence of perforation cannot be demonstrated roentgenographically either because the quantity of free air is minute or because the technic is faulty.

It is the purpose of this paper to present two cases showing an unusual roentgen sign indicative of intestinal perforation, without the characteristic presence of a visible amount of intraperitoneal air. Localization of the site of perforation was made possible by this same sign.

CASE I:[2] E. H., a 76-year-old white female, was admitted Sept. 11, 1946, with a history of a change in bowel habits of four months duration, consisting in increased frequency of defecation, inability to defecate completely, and a ribbon-like stool, occasionally bloody.

Urinalysis was negative. The Wassermann reaction was four plus.

Physical examination was essentially negative but for a large firm mass 3 inches above the rectal sphincter found on both digital and proctoscopic examination. The biopsy report was "adenocarcinoma of the rectum, colloid type."

On Sept. 20, there was onset of vomiting and abdominal pain. The abdomen was described as distended and slightly rigid.

Roentgenograms (Fig. 1) were interpreted as showing marked distention of the colon by fecal material. None of the signs of perforation was present. The patient was considered to be suffering from intestinal obstruction due to fecal impaction proximal to the tumor, and an attempt was made at decompression from below by means of enemata, but the results were poor. Her condition rapidly deteriorated and death ensued the evening of the same day.

At postmortem examination a considerable amount of free fecal material was found in the peritoneal cavity. An 0.8 × 0.3-cm. perforation was present in the anterior surface of the ascending colon, from which fecal material was oozing. The colon was dilated and filled with soft feces. When it was opened, two large shallow ulcerations were disclosed, having irregular margins and soft necrotic bases, one on the anterior surface of the mid ascending colon and the other at the splenic flexure, the former with a central perforation as previously described. The upper 8 cm. of the rectum was encircled by a large firm tumor with a narrow, tortuous lumen.

The anatomical diagnoses were: adenocarcinoma of the rectum with intestinal obstruction; acute colitis with perforation; acute peritonitis.

Comment: Upon review of the films it was noted that the fecal material, interpreted as contributing to the distention of the colon, actually did not conform to the usual colonic outline but represented spillage throughout the peritoneal cavity, particularly in the dependent portions.

CASE II:[3] P. T., a 70-year-old white male, was

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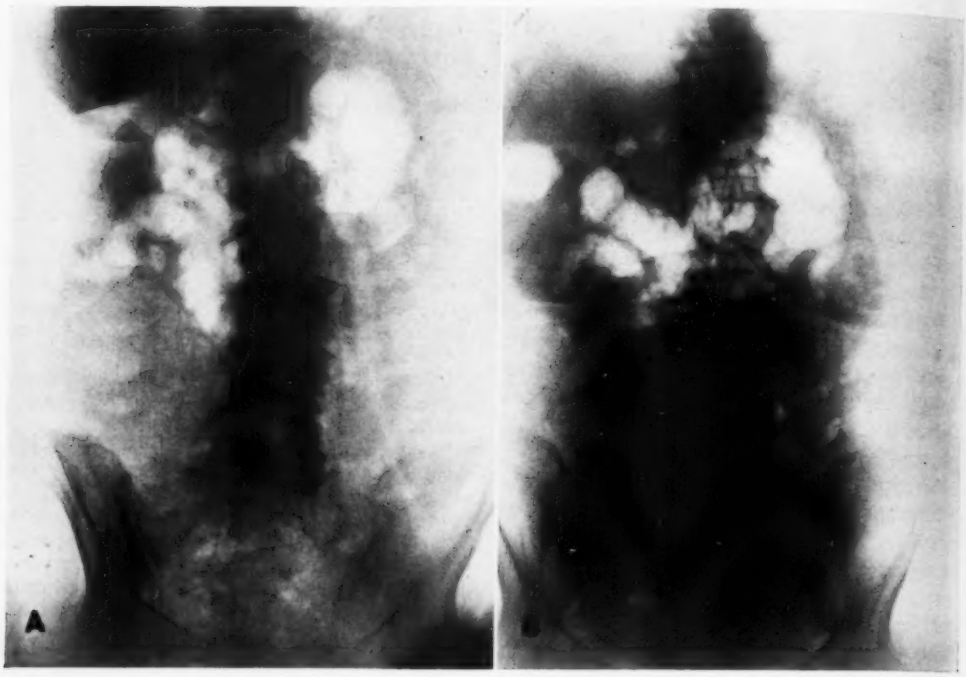

Fig. 1. Case I. Prone (A) and erect (B) roentgenograms showing appearance of fecal matter not conforming to the intestinal contour. Note absence of free air in peritoneal cavity.

admitted Oct. 1, 1946, with a one-year history of progressive dyspnea and orthopnea, occasional peripheral edema, and a 50-pound weight loss during the previous three months.

Physical examination was essentially negative but for diffuse right upper quadrant tenderness, a liver edge 4 cm. below the costal margin, and a blood pressure of 182/94.

The patient's private physician advised that an EKG had shown a left bundle-branch block and that he was on a maintenance dose of 0.1 gm. of digitalis daily. The admitting diagnosis was arteriosclerotic heart disease, and administration of digitalis was continued.

Two days after admission the patient began to complain of diffuse periumbilical pain, and the abdomen was found to be distended and tympanitic. Enemata were given, without relief.

A roentgenogram (Fig. 2) showed a large fluid level in the right upper quadrant, apparently within the lumen of the colon. In both the prone and erect films there was demonstrated a large amount of fecal matter, which was formless and did not conform to the usual structure of the colon. This fecal material apparently was free in the peritoneal cavity. On the basis of the observations in the previous case, a preoperative diagnosis was made of perforation of the colon.

At laparotomy the diagnosis was confirmed. The peritoneal cavity was found to be filled with feces; there was a perforation of the transverse colon, the distal portion of which was involved by a large mass. A cecostomy was performed and the peritoneal cavity drained. In spite of intensive supportive therapy, however, the patient died the same day.

Postmortem examination showed findings similar to those in Case I. The cecum and ascending colon were markedly distended and buried beneath fecal material. A 0.5-cm. perforation of the transverse colon was present, immediately proximal to a 3.0-cm. fungating annular tumor whose lumen would barely admit a finger tip. The remaining colon was normal in caliber and contained a small amount of feces.

The anatomical diagnoses were: carcinoma of the colon; acute peritonitis.

DISCUSSION

The diagnosis of perforation of the colon in the second case was made in consideration of the experience gained from the first case and was based upon the roentgenologic demonstration of fecal matter in the peritoneal cavity, not conforming to the expected outline of the colon.

The two cases were similar in that there

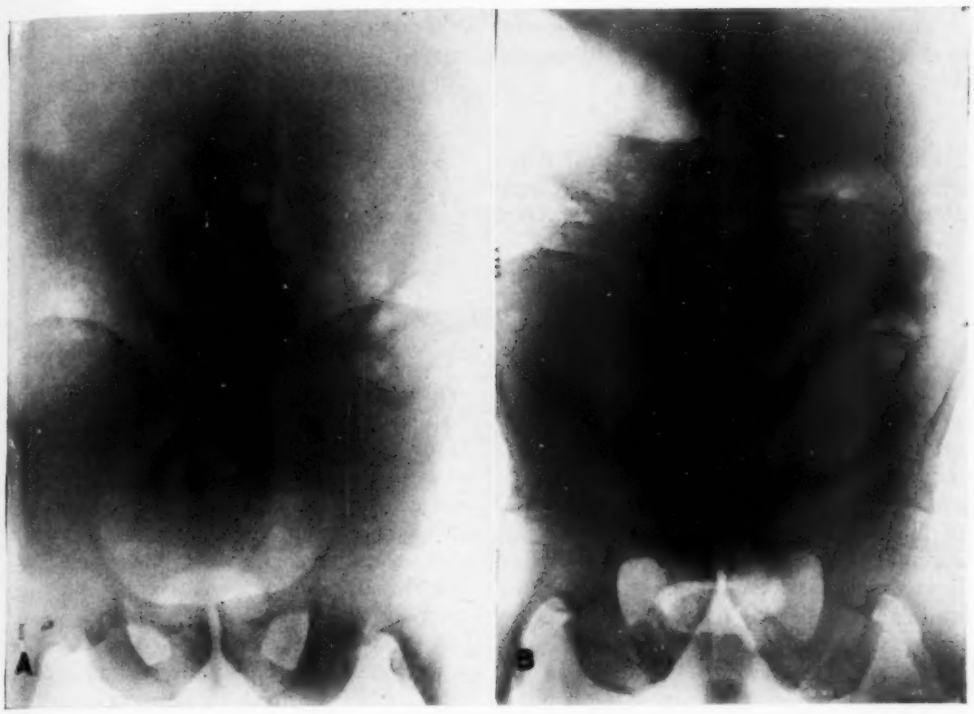

Fig. 2. Case II. Prone (A) and erect (B) roentgenograms showing formless fecal matter, as in Case I. A preoperative diagnosis of perforation of the colon was made because of this finding.

was not a sufficient amount of air outside the intestinal lumen to be roentgenologically demonstrable, nor were the secondary signs previously described of any value. In spite of this, it was possible to make a definite diagnosis of intestinal perforation and to localize the site of perforation to the colon.

Localization was possible because of the mottled granular appearance of fecal material, which is characteristic of the colon. (The enormous food residue occasionally seen in the mega-esophagus of achalasia may possibly simulate the appearance of feces roentgenologically, but this condition can hardly enter into the differential diagnosis.) It is noteworthy that in both cases perforation was secondary to a partial intestinal obstruction which had caused the accumulation of a large amount of feces proximal to the point of blockage. It would seem that this accumulation is essential in production of the sign, which in turn suggests its utility as evidence of perforation secondary to a gradual and partial obstruction of the colon. In the older age group represented by our cases, the obstruction is most commonly caused by a malignant tumor. It is generally accepted that in the great majority of patients with complete or partial colonic obstruction due to carcinoma, the lesion is in the left colon, and that 75 per cent of carcinomas of the left colon will be obstructive at some time in the course of the disease.

In view of these considerations, it is the authors' opinion that the roentgenologic demonstration of free fecal material in the peritoneal cavity, with or without the presence of extraluminal gas, is positive evidence of perforation of the colon, suggestive evidence as to the pathogenesis of the perforation, and perhaps of slight aid in localizing the point of obstruction. Obviously, localization by this means would pertain only to patients of the more

advanced age groups presenting a history of gradual partial or complete intestinal obstruction.

SUMMARY

Two cases of perforation of the colon are presented, with roentgenograms which were interpreted as showing free fecal material in the peritoneal cavity. The value of this sign in the diagnosis of intestinal perforation, even when free air is not demonstrable, is discussed.

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SUMARIO

Hallazgo Roentgenológico de Sumo Interés en la Perforación del Colon

Preséntanse dos casos de perforación del colon, en los que las radiografías revelaron materias fecales libres en la cavidad peritoneal. En ambos casos la perforación fué secundaria a una oclusión parcial debida a carcinoma, habiendo una gran acumulación de heces proximal al punto de obstrucción. Ni en uno ni en otro caso había suficiente aire fuera de la luz intestinal para demostración radiológica.

Los AA. señalan que la oclusión del colon en las personas de mayor edad, representadas en sus enfermos, es más habitualmente debida a carcinoma y que la mayoría de estas neoplasias radican en el lado izquierdo. A la luz de estas observaciones, opinan que la demostración radiológica de materias fecales libres en la cavidad peritoneal, con o sin la presencia de gas intraluminal, constituye prueba positiva de perforación del colon, prueba indicativa de la patogenia de la perforación y quizás de alguna leve ayuda en la localización del punto de la oclusión.

The Linear Atelectatic Sign in Intra-Abdominal Lesions[1]

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IT IS THE PURPOSE of this paper to call attention to the frequency of linear atelectasis in association with intra-abdominal lesions. Since 1936 (1) linear atelectasis has been adequately described in the roentgenologic literature. Nevertheless, even after a decade, many roentgenologists and clinicians fail to utilize this important diagnostic sign of intra-abdominal disease to the best advantage. Its presence, although not pathognomonic, should immediately lead to suspicion of a pathological condition within the abdomen. Among the terms by which horizontal linear atelectasis has been designated at various times are Fleischner's atelectasis (1, 2); disk, plate-like, or reflex atelectasis (3); lamelliform atelectatic foci.

HISTORICAL

Matthes (4), as far back as 1922, and subsequently Laurell (5) and Hultén (6) described the roentgenologic appearance of linear shadows in the lung bases which were secondary to underlying intra-abdominal lesions. These findings, however, they erroneously attributed to a fibrinous deposit on the pleura. Hultén (6) specifically cited 14 cases of acute pancreatic disease in which these linear shadows appeared. Haudek (7) in 1932, on the basis of pathological findings of pleuritis and parenchymal changes in the lung in association with upper quadrant abdominal disease, postulated that the thoracic lesions were due to a transmigrating pleuritis. Later, in 1934, Udvardy (8) reported similar changes in 8 cases of intra-abdominal disease and assigned them to the same cause. During the same period Klima and Pape (9) described the condition as atelectasis, though they had no autopsy proof.

It remained for Felix Fleischner (1), in 1936, to set forth adequately the present-day conception of the physiopathology of linear atelectasis, on the basis of two autopsied cases. Two years later, Oppenheimer (10) reported a case coming to autopsy and confirmed Fleischner's finding that the linear shadows corresponded to atelectasis and were not due to pleural thickening.

ROENTGENOLOGICAL DESCRIPTION AND DIFFERENTIAL DIAGNOSIS

Pathologically the atelectatic area is discoid in shape, lying in more than one plane of the lung. The resulting roentgen appearance is that of either a single striation or multiple striations rather than a solitary area of homogeneous density. Frequently the striations extend from the cardiac border to the peripheral lung fields in a horizontal or oblique direction. When oblique, they radiate in a direction not parallel but rather perpendicular to the interstitial markings of the lower lung fields. The striations vary from thread-like lines to bands which may measure as much as half a centimeter in thickness. The majority, however, are of narrow caliber. Linear atelectasis is usually found in the lower third of the lung fields, either unilaterally or bilaterally. Most frequently it is seen immediately above the diaphragm. The latter structure is generally elevated and fluoroscopically reveals limitation of motion (Figs. 1 and 2).

Fleischner, Hampton, and Castleman (11) have clarified the differential diagnosis of linear shadows in the lung through

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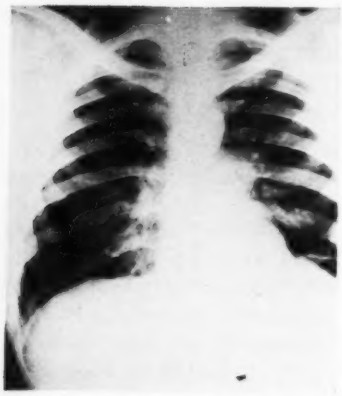

Fig. 1. Case 14: Gastric carcinoma with hemorrhage. A linear zone of atelectasis is present in the lower fourth of the left lung.

the correlation of the roentgen findings with autopsy studies. These authors differentiate linear atelectasis from such lesions as interlobar pleuritis, healed pulmonary infarcts, and the residua of old destructive infections. Linear atelectasis, as opposed to interlobar pleuritis, does not correspond to the fissure levels. In lateral and oblique projections plate-like foci are roughly perpendicular to the longitudinal fissure. The shadows of infarcts are usually single and shorter than linear atelectatic areas and may take any direction in contrast to the constant horizontal character of this specific type of atelectasis. The infarct shadows persist, show no change on diaphragmatic movement, and may occur in any portion of the lung.

PHYSIOPATHOLOGY

Linear atelectasis is always secondary to some other lesion, either intrathoracic or intra-abdominal. When these primary pathological conditions (intra-abdominal lesions) produce shallow breathing due to diaphragmatic inflammation or elevation of the diaphragm, abnormal bronchial secretions may occur, resulting in the plugging of a bronchus. When this happens in peripheral bronchi or bronchioles, linear atelectasis develops. Plate-like atelectatic foci occur in a horizontal direction, according to Fleischner, because of the relative fixation of the mediastinum medially and the negative intrapleural pressure peripherally. This mechanism prevents vertical collapse in the presence of a small obstructed area. As the atelectasis occurs following bronchial or bronchiolar obstruction, the normally elastic alveoli immediately above and below become emphysematous, permitting the collapse to occur in a horizontal direction.

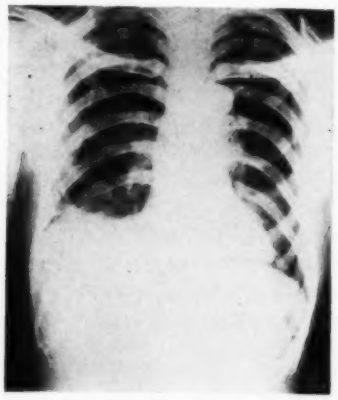

Fig. 2. Case 20: Intra-abdominal tumor. The linear zone of atelectasis is in the lower one-fourth of the right lung. In this case the roentgen findings preceded any other evidence of an intra-abdominal lesion.

The following intra-abdominal lesions are among those which have been cited as etiological factors in linear atelectasis:

Inflammatory Lesions
- Liver abscess (6)
- Subdiaphragmatic abscess (1)
- Acute cholecystitis (10)
- Subacute pancreatitis (6)
- Acute pancreatitis (5, 6)
- Periappendiceal abscess (6)
- Perforated peptic ulcer (5)

Neoplasms
- Ovary (6)
- Gallbladder (6)
- Ileum (6)
- Transverse colon (5)

Miscellaneous Lesions
- Hepatic cirrhosis (5, 6)
- Incarcerated abdominal hernia (5)

AUTHORS' SERIES

A total of 9,487 chest roentgenograms were utilized in the series of cases to be reported here. Routine examinations of

TABLE I: OBSERVATIONS IN TWENTY-SIX CASES OF LINEAR ATELECTASIS

Case No.	Diagnosis	Method of Diagnosis	Right Side		Left Side		Mediastinal Shift	Subsequent Roentgenogram
			Elevation of Diaphragm	Linear Atelectasis	Elevation of Diaphragm	Linear Atelectasis		
1	Cirrhosis	Biopsy	x	x	0	0	0	Negative in one month
2	Cirrhosis	Clinical	x	x	0	0	0	Negative in ten months
3	Cirrhosis with ascites	Biopsy	x	x	x	x	0	Atelectasis present at three weeks
4	Cirrhosis with ascites	Biopsy	0	x	0	x	0	Original involvement of left side. Bilateral at 3 months
5	Cirrhosis with ascites	Clinical	x 0	x 0	0 0	0 x	0	Atelectasis disappeared on right. Appeared on left at 2 months
6	Cirrhosis with ascites	Clinical	x x	x x	0 x	0 x	0	Original involvement on right only. Bilateral at 6 weeks
7	Cirrhosis with tbc. peritonitis	Autopsy	x	x	0	x	0	....
8	Acute cholecystitis with perforation	Surgical	0	x	0	0	0	....
9	Chronic cholecystitis	Surgical	x	x	0	0	0	....
10	Carcinoma of gallbladder	Autopsy	x	x	0	0	0	....
11	Subdiaphragmatic abscess	Surgical	x	x	0	0	0	Effusion on right
12	Metastatic carcinoma of liver	Surgical	x	x	0	0	0	Effusion on right
13	Gastrojejunal ulcer, perforated	Surgical	x	0	x	x	0	....
14	Gastric carcinoma with hemorrhage	Autopsy	0	x	x	x	0	Negative in one month
15	Perforated peptic ulcer, postoperative	Surgical	0	x	0	0	0	....
16	Perinephritic abscess (right)	Autopsy	0	x	0	0	0	....
17	Acute necrotizing pancreatitis	Autopsy	x	x	0	0	0	....
18	Perforated appendicitis, postoperative	Surgical	x	x	0	0	0	....
19	Strangulated inguinal hernia (right), peritonitis	Autopsy	0	0	x	x	0	Atelectasis present after two weeks
20	Degenerating tumor (left side of abdomen)	Biopsy	x	x	0	0	0	....
21	Septic abortion	Clinical	x	x	0	0	0	Negative in two weeks
22	Incarcerated umbilical hernia	Clinical	x	x	0	0	0	....
23	Stab wound (left hemithorax)	Surgical	0	0	x	x	0	....
24	Herpes zoster (right chest)	Clinical	x	x	0	0	0	....
25	Acute bronchitis	Clinical	0	0	x	x	0	Atelectasis absent after 7 days
26	Right-sided phrenic exeresis	Surgical	0	0	x	x	0	....

nurses, physicians, employees, and others who were not either hospital or dispensary patients accounted for 2,423 of these. In this group no instance of linear atelectasis was encountered. The remaining 7,064 roentgenograms represented patients hospitalized for complaints of all types. In 29, or 0.4 per cent, of this number linear atelectasis was demonstrated. Three of the 29 cases were excluded from the series

because no adequate primary source either intra-abdominal or extra-abdominal could be demonstrated. Of the 26 cases remaining, 22 were proved by surgery, biopsy, autopsy, or unquestionable clinical findings to have an associated intra-abdominal lesion. The other 4 (20 per cent) were best explained as due to a thoracic lesion.

Total consecutive chest roentgenograms	9,487	
Routine examinations (nurses, physicians, employees, etc.)	2,423	
Hospitalized cases	7,064	
Linear atelectasis demonstrated	29	(0.4%)
Cases excluded because no associated intra-abdominal, or intrathoracic lesion was demonstrable	3	
Remaining cases of linear atelectasis	26	(100%)
Associated with intra-abdominal lesions	22	(80%)
Associated with intra-thoracic lesions	4	(20%)

Our cases (Table I) usually showed an elevation of the diaphragm in association with the atelectasis. In the presence of cirrhosis without ascites, the linear atelectasis was right-sided. With ascites, it was found to be bilateral. The atelectasis occurred in 12 cases on the side of the corresponding involved organ; in 3 cases on the opposite side. It was transient in character, but at times persisted for weeks and even months. Although others have mentioned a mediastinal shift, we failed to demonstrate this finding.

SUMMARY

A series of 26 cases of linear atelectasis is presented. Although small, it is believed to be significant because of the high incidence of associated intra-abdominal disease (80 per cent). In the past, diaphragmatic elevation has been utilized frequently as a sign of either an intrathoracic or an intra-abdominal lesion. In many instances, the primary lesion has proved to be intrathoracic. The presence of linear atelectasis, however, either with or without a high diaphragm, affords presumptive evidence of disease within the abdomen.

NOTE: We wish to thank Dr. G. E. Gutmann for his help in the translation of the foreign references.

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SUMARIO

El Signo de la Atelectasia Lineal en las Lesiones Abdominales

En una serie de 7,064 radiografías torácicas de enfermos hospitalizados con síntomas muy variados, encontráronse 29 casos (0.4 per ciento) de atelectasia lineal. En 3 de ellos no se descubrió la lesión primaria que ocasionaba la atelectasia. De los otros 26, en 22, o sea 80 por ciento, había asociación con una lesión intraabdominal primaria, en tanto que 4, o sea 20 por ciento, eran imputables a enfermedad intratorácica.

En el pasado, la elevación del diafragma ha sido utilizada frecuentemente como signo de lesión ya intratorácica o intraabdominal. La presencia de atelectasia lineal, con o sin elevación del diafragma, parece ofrecer prueba presuntiva de afección intraabdominal.

Dysgerminoma

Case with Pulmonary Metastases; Result of Treatment with Irradiation and Male Sex Hormone[1]

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PULMONARY METASTASES from dysgerminoma have seldom if ever been reported in a living patient. The case to be presented here is of interest as showing such metastases and further in that administration of male sex hormone (testosterone propionate) produced remarkable palliation for about two years, the tumor retaining its radiosensitivity after that period. For these and other reasons we believe the case to be worthy of record.

CASE REPORT

A white female aged 48 was first admitted to University Hospitals on Aug. 3, 1939, complaining of pain in the lower abdomen. An appendectomy had been performed in another hospital in 1937, and a wound infection at that time had drained for thirty days. Three months later a cul-de-sac drainage of a pelvic abscess was done. Since then the patient had suffered repeated attacks of low abdominal pain, lasting eight or nine days, accompanied by nausea, vomiting, frequency and incontinence of urine.

The patient was married and the mother of ten children, all living, ranging in age from nine to twenty-nine years. Menstruation had begun at the age of fourteen and had occurred regularly every twenty-eight days, the periods lasting three to four days, with an average flow. The last period had occurred six years prior to this admission.

Examination revealed a pelvic mass which extended almost up to the level of the umbilicus, tense and extremely tender to palpation. Bimanual examination showed the cervix to be free of disease but somewhat fixed. The uterus itself could not be clearly outlined, due to the presence of large nodules in both adnexa and a mass about 8 cm. in diameter in the cul de sac. Other organs appeared to be normal.

At operation on Aug. 23, 1939, both ovaries were found to be enlarged, the right measuring about 15 cm. in diameter and the left 8 cm. Sharp dissection was necessary to free these masses from the adjoining parietal peritoneum and small intestines. The uterus was about twice normal size, but contained no apparent fibroids. A supracervical hysterectomy and bilateral salpingo-oophorectomy was done.

Fig. 1. Pulmonary metastasis in right lung when first detected, April 7, 1942.

The mass previously described in the cul de sac proved to be the left ovary.

Microscopic sections of the ovarian tissue were examined by Dr. Hugh Jeter, who made a diagnosis of malignant dysgerminoma. Dr. Fred Adair and Dr. Emil Novak, who were requested to examine these tissues, expressed a similar opinion.

The patient made an uneventful recovery, and postoperative irradiation was begun in the third week, through eight fields, four over the abdomen and an equal number over the back. A total dose of 900 r, in air, was given to each field, with the following factors: 200 kv., Thoraeus filter, 50 cm. distance, daily dose 300 r to one field.

On a routine chest film taken April 7, 1942, a small discrete nodule about 2 cm. in diameter was noted in the right middle lung field (Fig. 1).

The patient got along fairly well for about three and a half years, when she was again admitted because of two painful subcutaneous masses, one on the anterior aspect of the thigh and the other in the left axilla. The nodule in the thigh was excised and proved microscopically to be similar to the original tumor. The axillary metastasis was irradiated, showing about 50 per cent regression after a dose of 2,400 r, in air, to this area. The pulmonary metastasis had doubled in size since it was first observed.

[1] From the Departments of Radiology and Gynecology, University Hospitals, Oklahoma City, Okla. Accepted for publication in March 1948.

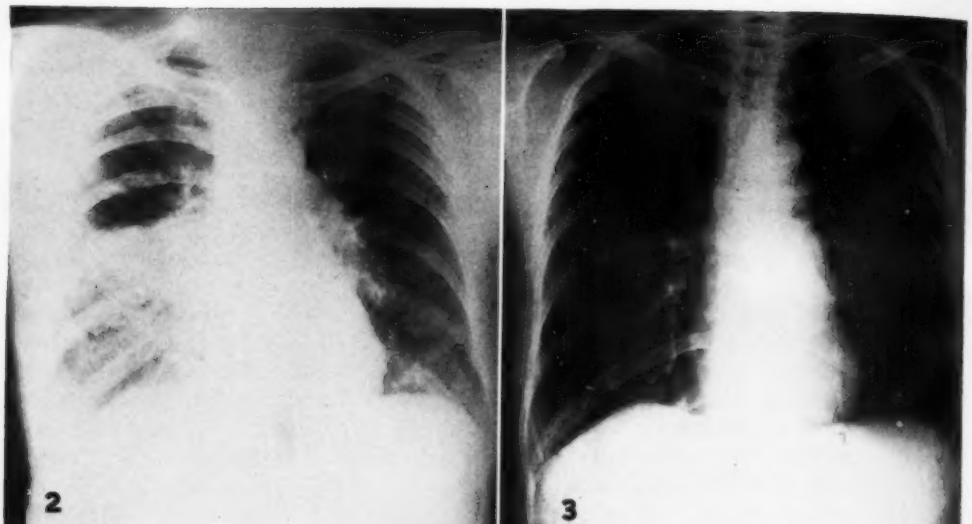

Fig. 2. Metastases in both lungs and mediastinum, which developed during treatment with male sex hormone Aug. 7, 1945.
Fig. 3. Regression of metastasis in right lung following deep x-ray therapy. Mediastinal involvement more easily seen. Dec. 5, 1945.

The patient's condition remained stationary for about five months, but on a return visit, on Aug. 30, 1943, her complaints again were of a serious nature. Hematuria had developed, and she complained of severe pains in the left upper quadrant of the abdomen. A retrograde pyelogram revealed an enlarged left kidney, with distortion of the superior major calix, which was interpreted as being due to metastasis. Because of the poor general condition and multiple metastases, it was decided to give a trial period of male sex hormone therapy. Treatment was begun with 25 mg. of testosterone propionate daily by intramuscular injection. The favorable response to this form of treatment warranted its further use, and for the next two years the patient was carried on a maintenance dose of about 30 mg. a week, 10 mg. being administered every other day. During this period no other form of treatment was given, but the weekly dose was increased whenever certain symptoms became aggravated. The patient maintained her average weight, and no analgesics or narcotics were necessary to tide her over her bad spells. She became bedfast on several occasions, notably when injections were purposely withheld or when, for various other reasons, they were omitted.

During this two-year period the pulmonary metastasis slowly grew larger and other metastases were noted in the liver and right kidney. Later, metastases appeared in the left lung and mediastinum (Fig. 2). Toward the end of the two years the beneficial effects of the hormone therapy became less and less, so that x-ray therapy was again instituted since it had had some effect previously (Fig. 3).

The patient was last seen in our clinic a month before her death on June 26, 1946, a little over seven years after her first visit. Necropsy was not obtained.

DISCUSSION

Since 1931, when Meyer first used the designation dysgerminoma for the ovarian counterpart of the testicular seminoma, well over 300 cases have been reported. Only about 10 per cent of these, however, have occurred in women past the age of forty. This type of ovarian tumor is often associated with sexual underdevelopment or pseudohermaphroditism, although in about half the cases no sexual abnormalities exist. In about 35 per cent of the cases both ovaries are involved (1, 5). Our patient was a women forty-eight years old who had ten living healthy children, indicating normal sexual development.

Since the degree of malignancy cannot be accurately evaluated from the microscopic appearance of the tumor, one must depend upon the gross findings at the time of operation. Involvement of one or both ovaries with the neoplasm well encapsulated carries a good prognosis. If invasion of the surrounding peritoneum has

taken place and the tumor is adherent to surrounding organs, the outlook is less favorable. The presence of metastases in lymph nodes and distant organs warrants a grave prognosis and only palliation can be offered (3). The operator in the case here reported (J. W. K.) recorded that the tumor masses had to be dissected from peritoneum, rectum, and small intestine, though no other metastases could be detected at that time. In spite of the invasiveness of the tumor, the patient survived for over seven years.

The radiosensitivity of dysgerminoma has been reported by various authors as comparable to that of lymphoid and myeloid tumors (2). Certain cases less responsive to irradiation have, however, also been recorded. In our patient only 50 per cent regression was noted after fairly heavy dosage to a superficial lesion in the axilla. This was one reason which led us to try the effect of male sex hormone. The other reason was the multiplicity of metastases and the poor general condition of the patient, which made it doubtful in our minds whether she could tolerate adequate irradiation therapy.

Hormone studies done by others have yielded negative results (6). Since dysgerminomas, according to Meyer, are composed of fetal gonad tissue prior to sex differentiation, sex hormone production would not be compatible with the histogenesis of the tumor. The prompt response of our patient to male sex hormone therapy appears to warrant further studies in similar cases in relation to sex hormone production. After the first ten injections of testosterone propionate the improvement noted was so remarkable and steady that it was decided to continue this form of therapy. After two years the palliative effect slowly became less and less, so that we again had to resort to deep x-ray therapy.

Metastases from dysgerminoma are usually confined to the pelvic, abdominal, and retroperitoneal organs (6). Involvement of the more distant parts of the body has only rarely been reported, although it may occur more often than recorded. Pendergrass recently reported a case in which an intraorbital mass was the first clinical symptom. A biopsy did not establish the true nature of the lesion. Later, metastases in the skeleton developed to such an extent as to produce a pathological fracture. At necropsy, bilateral involvement of the ovaries was found, with metastases in the spinal column, thymus and lungs (4).

Invasion of pulmonary tissue by dysgerminoma has only rarely been demonstrated in the living patient. In our case a pulmonary lesion was first noted on a chest film taken some two years and eight months after operation for the primary tumor. We were able to follow the progress and growth of this lesion for four years. Later mediastinal involvement could be demonstrated, with invasion of the opposite lung. The lung metastases regressed less than 50 per cent following a series of deep x-ray treatments. Other metastases discovered on physical or radiographic examination involved the superficial and deep chains of lymph nodes, subcutaneous tissues, liver, and both kidneys.

CONCLUSION

A case of dysgerminoma is reported, occurring in a 48-year-old white woman, who survived seven and a half years after removal of the tumor followed by deep x-ray irradiation and male sex hormone therapy.

Radiosensitivity of this particular tumor was not remarkable. Good palliation was obtained with the administration of the male sex hormone over a two-year period, after which time it became much less beneficial.

Pulmonary metastases were present and were studied for a period of approximately four years. Other metastases occurred in the supraclavicular, inguinal, abdominal, mediastinal, and retroperitoneal lymph nodes, the kidneys, and the liver.

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SUMARIO

Disgerminoma: Caso con Metástasis Pulmonares. Resultado del Tratamiento con la Irradiación y la Hormona Masculina del Sexo

Comunícase un caso de disgerminoma, observado en una mujer de 48 años, que sobrevivió siete años y medio la extirpación del tumor, seguida de la roentgenoterapia profunda y del tratamiento con la hormona masculina del sexo (propionato de testosterona).

La radiosensibilidad del tunor no fué notable. Obtúvose buen efecto paliativo con la administración de la hormona masculina durante un período de dos años, pero dejando para entonces de ser eficaz.

Las metástasis pulmonares fueron observadas por primera vez más de dos años después de la extirpación del tumor primario, y la evolución de las mismas fué observada durante unos cuatro años. Otras metástasis sobrevinieron en los ganglios linfáticos supraclaviculares, inguinales, abdominales, mediastínicos y retroperitoneales, y en los riñones y el hígado.

The Hematological Effects of Ionizing Radiations[1]

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THE OBJECTIVES of the Health Division of the Plutonium Project were essentially (*a*) to study the fundamental and comparative biological action of external radiations and internally administered radioactive materials, (*b*) to apply the findings for the protection of individuals who worked in the Project, and (*c*) to use the findings generally for the protection of the public which was potentially in danger of exposure to these physical hazards.

The hematologic studies[2] conducted on the Plutonium Project were divided into four main categories, namely, the effects of acute[3] whole-body exposure to externally administered penetrating radiation, the effects of chronic[4] whole-body exposure to externally administered penetrating radiations, acute toxicity of parenterally and enterally administered radioactive compounds, and chronic toxicity of parenterally and enterally administered radioactive isotopes.

In order to correlate properly studies on the peripheral blood effects with those occurring in the hemopoietic tissue, the animals in the same or parallel experiments were sacrificed at intervals for histologic study. All experiments included an adequate number of controls, and the frequency of sampling depended upon the chronic nature of the experiment.

COMPARATIVE EFFECTS OF ACUTE WHOLE-BODY EXPOSURE TO X-RAYS AND FAST NEUTRONS

In considering the irradiation of the whole body with penetrating radiations of external origin, those of significance in so far as *direct* effects on the blood and blood-forming tissue are concerned are x-rays, gamma rays, fast neutrons, and slow neutrons. The beta and alpha rays that originate from radioactive substances can largely be neglected, because penetration in tissue is only a few millimeters in the former and a fraction of a millimeter in the latter. The studies on animals by Raper and Barnes (1), Raper, Zirkle, and Barnes (2), Raper, Henshaw, and Snider (3), and others, have demonstrated that, although beta rays may penetrate the skin, the hematologic effects, if any occur, are minimal and are secondary to other more serious pathological changes. No experiments similar to those of Raper and Zirkle have been performed using alpha rays. Since alpha rays have such shallow penetrability (*e.g.*, those emitted by plutonium or radium will penetrate only about 40 μ into the skin), no direct effects and only minimal indirect effects on hemopoietic tissue appear likely.

Studies on the effects of acute exposure of animals to a slow neutron flux have been carried out by Zirkle (4*a*). This slow neutron source, however, was contaminated with fast neutrons, and the effect on the hemopoietic system, as reported by Raper, Henshaw, and Snider (3), is therefore difficult to interpret. As has been pointed out by Zirkle (4*a*, *b*), however, it is not the slow neutron itself that produces biological effects, but rather the gamma rays and fast atomic nuclei emitted upon nuclear cap-

[1] From the Argonne National Laboratories, the Department of Medicine of the University of Chicago, and the National Cancer Institute of the United States Public Health Service. This document is largely based on work performed under Contract No. W-704-eng-37 for the Atomic Energy Commission at the University of Chicago. Accepted for publication in August 1948. Presented in part at the Thirty-fourth Annual Meeting of the Radiological Society of North America, San Francisco, Calif., Dec. 5–10, 1948.

[2] This manuscript reviews hematologic studies initiated during the war, many of which are still under active investigation. It is not intended as a review of the literature, but rather to summarize studies of interest which are to be reported in the National Nuclear Energy Series (NNES).

[3] Single exposure.

[4] Repeated exposures.

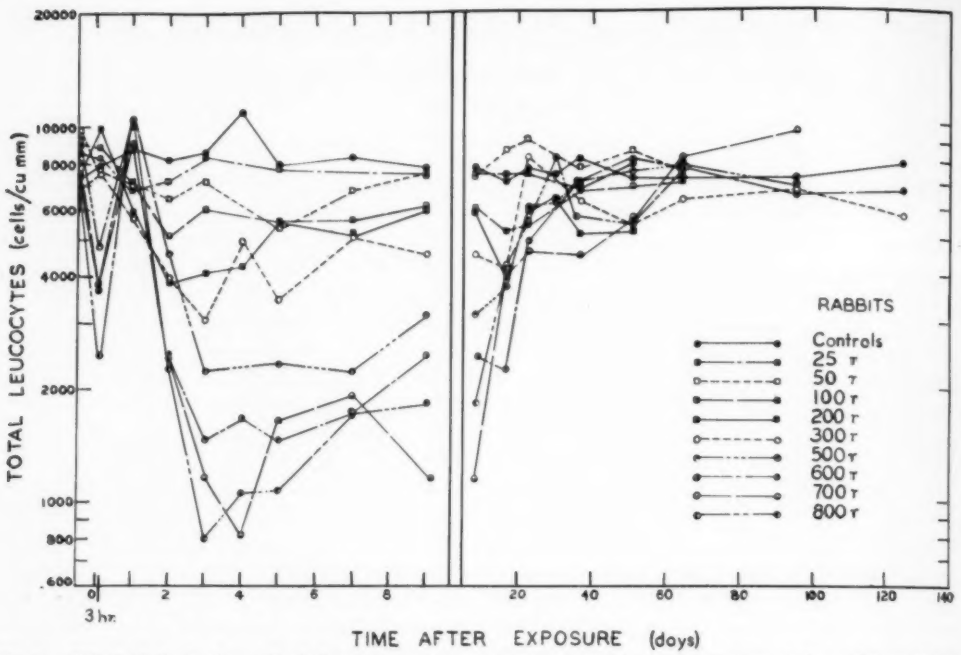

Fig. 1. Effect of single doses of whole-body roentgen radiation on the leukocyte values of the peripheral blood of rabbits.

ture of the slow neutron in certain elements within the body. It is likely, therefore, that the exposure of experimental animals or man to a pure slow neutron flux would produce biological effects comparable to those induced by gamma rays plus fast neutrons. Henshaw, Snider, *et al.* (5) conducted studies in which relatively heavy doses of gamma rays (*i.e.*, 500 and 700 r) were given to mice in one acute exposure within a period of minutes. Though hematologic studies were not adequate to make a comparison with x-ray effects, the biological action of gamma rays and penetrating x-rays can be expected to be qualitatively the same.

Acute Exposure to Penetrating X-rays

The whole-body exposure of rabbits, rats, mice, chicks, human beings, goats, guinea-pigs, and dogs to roentgen radiation given in one dose has revealed that in terms of sensitivity of the blood and blood-forming tissue these animals may be listed as above in appropriate order of increasing sensitivity (6–12).

The x-rays administered in these experiments were generated in a 200-kv. machine operating at 15 ma. A 0.5-mm. copper filter and a 1.0-mm. aluminum filter were used. The half-value layer in copper of the filtered beam was 0.98 mm. The exposures were measured with a Victoreen condenser r-meter equipped with a 100-r chamber. Measurements were made in air within a treatment box at the position occupied by the center of the animal's body. Victoreen chambers of 250 r full-scale reading were used as monitors. For rats, the dose rate at 84 cm. averaged 12 r per minute; for rabbits 12–16 r at 87.5 cm.; for mice, 15 r at 79 cm.; for guinea-pigs, 12 r at 86 cm.; for dogs, 6 r at 107 cm.; for goats, 3.3 r at 132 cm. As pointed out, the doses given are those in the center of the animal's body, measured in air. Thus, the average tissue dose received by the body of the mouse will be approximately the same as the air dose; for guinea-pigs and rats, it will be slightly smaller; for the larger animals, it will not only be considerably smaller, but also the actual doses received

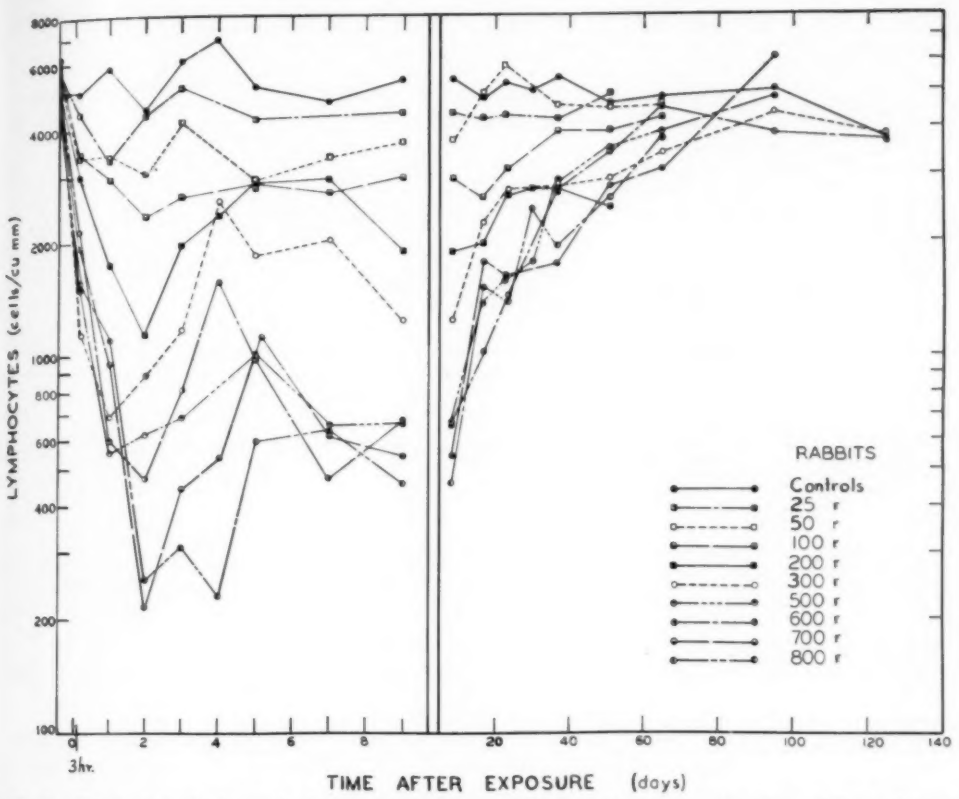

Fig. 2. Effect of single doses of whole-body roentgen radiation on the lymphocyte values of the peripheral blood of rabbits. With doses of 200 r and above, a temporary elevation in the lymphocyte values occurs between the second and ninth day after irradiation ("abortive rise").

by the various tissues will differ to some extent. To obtain more uniformly distributed dosage, the larger animals were given one-half of the total dose to one side and the other half to the other side (13).

The most sensitive indicator of radiation effect in any of these species that can be recognized by a study of the peripheral blood is a reduction in the number of total lymphocytes per cubic millimeter. In general, this effect is not significant in these species with doses below 25 r. The general pattern of acute radiation response of the leukocytes in the peripheral blood of the rabbit is shown in Figures 1 and 2. Lymphocyte values fall below control values after 25 r and return to normal limits within twenty-four to forty-eight hours. With doses of 100 r and above, a reduction occurs after three hours and a maximum depression is reached by twenty-four to forty-eight hours. Recovery proceeds slowly, requiring more than sixty days with doses of 300 r and above. After irradiation, the monocytes of the peripheral blood initially follow a pattern of response similar to the lymphocytes but characteristically return to normal values or show an absolute increase between the fourth and sixth day after exposure to 100 r and above. An increase in the neutral red granules of the lymphocytes is observed after doses of 600 r. An increase in heterophil motility, after twenty-four hours, is observed following doses of 200 r and above.

A significant initial rise in absolute heterophil[5] values in the peripheral blood of the rabbit follows a dose of 400 r and above. After doses of 500 and 800 r, two

[5] Neutrophil in man.

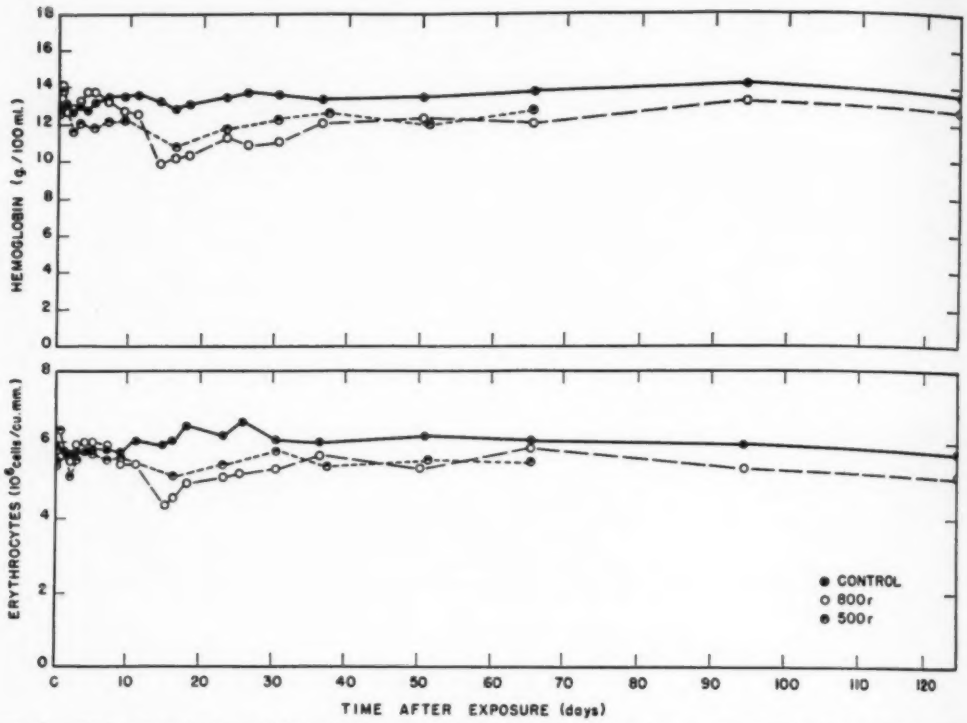

Fig. 3. Effect of single doses of 500 and 800 r whole-body roentgen irradiation on the hemoglobin and erythrocyte values in the peripheral blood of rabbits.

initial peaks at about twelve and twenty-four hours are observed. No significant reduction in heterophil values occurs with doses of 300 r and below. After 400 to 800 r, a significant reduction in heterophils is apparent after ninety-six hours, with recovery to normal limits by twenty-three days or less.

The platelet values of the peripheral blood, as indicators of acute x-ray damage of the hemopoietic system, are comparable to the granular series except that reduction occurs later. In the rabbit, platelets are greatly reduced after doses of 500 or 800 r, reaching a minimum on the eighth day after exposure. Recovery follows usually within one or two weeks. Gross bleeding and microscopic bleeding into the skin and other tissues are quite apparent in rabbits after doses of 500 to 800 r. This is due in part to the platelet reduction and capillary abnormality, but the hyperheparinemia described by Allen *et al.* (14*a*, *b*, *c*, *d*) probably plays a role in the process.

No anemia of significance has been observed in groups of rabbits on the basis of mean averages with dosages below 500 r in an acute exposure to the whole body. In an occasional animal a slight anemia developed after exposure to 300 r. A progressively larger fraction of experimental animals showed anemia after 500, 600, 700, and 800 r. An acute dose of 800 r produced a significant normochromic anemia that reached a maximum at fourteen days, with recovery by the twenty-third day. Figure 3 illustrates the anemia that develops after 800 and 500 r. Many of the animals that succumbed within the first three weeks after receiving doses of 600 to 800 r died with severe terminal anemia of a relatively abrupt onset.

Reticulocytes are not reduced significantly in the peripheral blood of rabbits receiving doses below 100 r. Above this

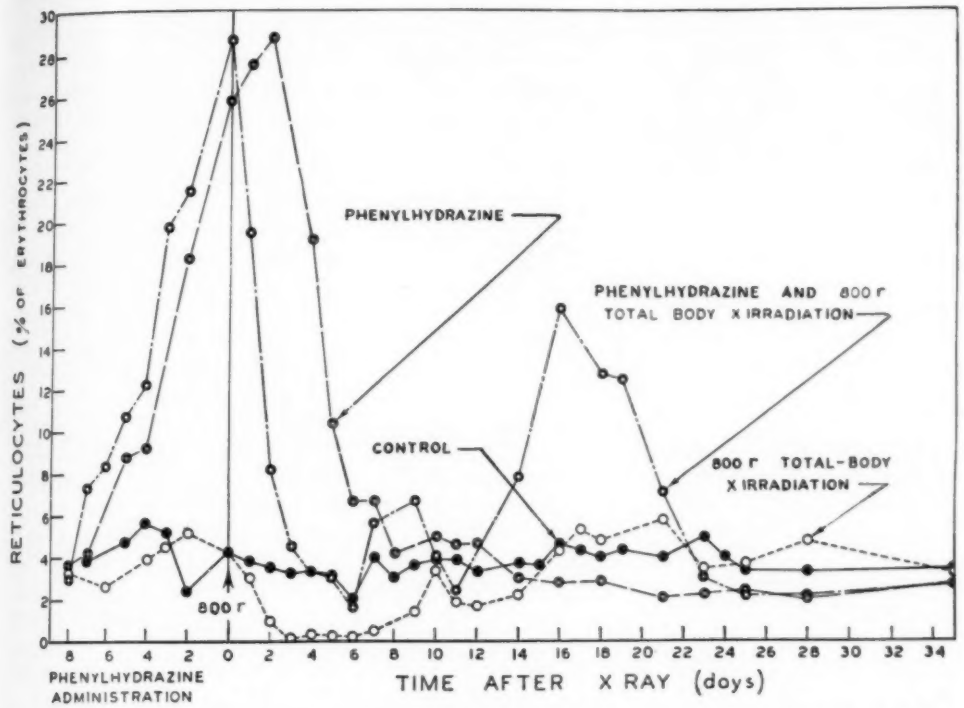

Fig. 4. Effect of a single dose of 800 r whole-body roentgen irradiation on the reticulocyte values in the peripheral blood of normal rabbits and rabbits with a phenylhydrazine-induced anemia. (Originally published in Science 107: 248, 1948)

level, the degree of depression becomes significantly greater with increasing doses. After the exposure of rabbits to 800 r, the reticulocytes fall from a normal value of 3 to 5 per cent to less than 0.1 per cent by seventy-two hours, and, as is shown in Figure 4, recovery proceeds slowly during the first fourteen days and normal values are reached by twenty-three days.

The effects of x-rays upon the cellular constituents of the peripheral blood of the rabbit typify the pattern of response in rats, mice, guinea-pigs, dogs, man, goats, and chickens, with certain exceptions. The anemia produced in rabbits after an $LD_{50}/30$ days[6] whole-body exposure is usually normochromic. In other species, particularly the rat and man, a definite macrocytic anemia may develop (7, 10). The LD_{50} dose for rabbits is approximately 800 r; for rats, 600 r; for dogs, 315 r; for mice, 540 r; and for goats, 350 r. These data, of course, hold only for the animals used in these experiments. There may be considerable differences in the LD_{50} dose for different strains or hybrids of the same species. The effect of 800 r on rabbits is thus roughly comparable to the effect of 315 r on dogs. A difference of recovery rates exists between species, however. The extreme example of this difference in recovery rate is seen when one compares the rabbit and the rat. The rat recovers much more rapidly than the rabbit after comparable irradiation damage.

(*a*) *Abortive Rise in Leukocytes and Reticulocytes After Acute Exposure:* Between the second and eleventh day after irradiation of the rabbit with 200 r or more, an "abortive rise" in reticulocytes, lymphocytes, and heterophil values of the peripheral blood occurs. This phenomenon as it involves the lymphocytes is

[6] Hereafter referred to as LD_{50}.

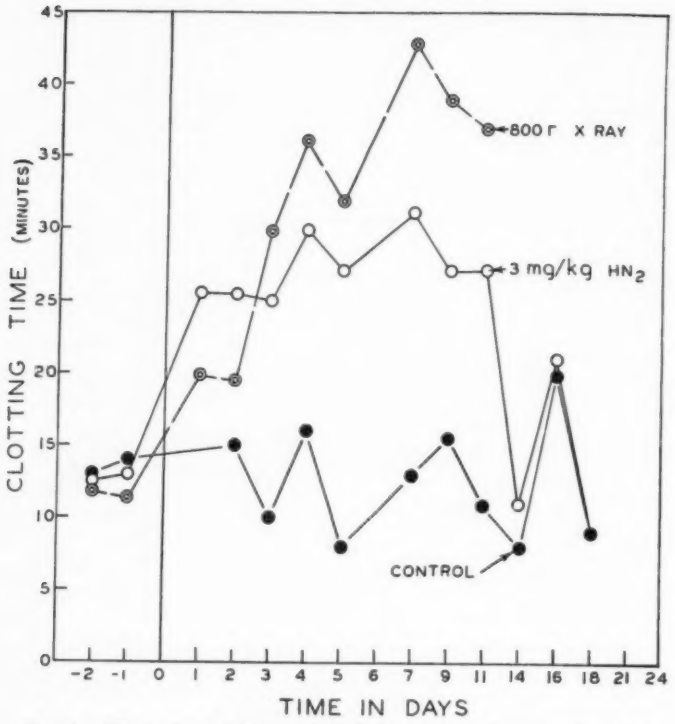

Fig. 5. Effect of a single injection of nitrogen mustard (methyl bis(β-chloroethyl) amine hydrochloride) in a dose of 3.0 mg. per kilogram of body weight and a single dose of 800 r whole-body roentgen irradiation on the whole-blood coagulation time (Lee White) of rabbits. (Originally published in J. Lab. & Clin. Med. **33:** 1560, 1948)

illustrated in Figures 2 and 9. As to its nature, only speculation is possible. It may be related to the "waves of regeneration" that are seen histologically in the hemopoietic tissue of irradiated animals that have been described by Bloom and his associates (8) and by Jacobson and Block (15). The fact that grossly abnormal forms, especially of the myeloid series, are seen both in the peripheral blood and bone marrow during this period, followed by a recurrent wave of degeneration, suggests that this "abortive rise" actually represents effects produced at the time of irradiation in the precursors, which after a series of divisions no longer survive.

(*b*) *Studies on the Effect of Penetrating Radiations on Coagulation of Blood:* A prolonged bleeding time, increased capillary fragility, thrombocytopenia, and prolonged clotting time have been described following heavy acute exposures of animals to roentgen radiation by Shouse, Warren, and Whipple (16), whose findings have been confirmed by Jacobson, *et al.* (12, 14*c*). The explanation for a prolonged bleeding time was considered to be related to the thrombocytopenia; neither the increased capillary fragility nor the prolonged clotting time had been adequately explained. Allen, Jacobson, *et al.* (14*a*, *b*, *d*), working with dogs, have shown that this increased clotting time is definitely related to an increase in the amount of a circulating heparin-like substance and is a major cause of death from acute irradiation injury. This anticoagulant increase may be sufficient in certain dogs to render the blood incoagulable in the test tube. The anticoagulant present in the blood of some of these animals is sufficient to alter the coagulability of the blood of normal animals

in the test tube. This hemorrhagic state can be repeatedly reversed for varying periods of time (twenty-four to seventy-two hours) by administration of purified toluidine blue, protamines, and certain of the thionin dyes. The hemorrhagic state has been found to occur in other mammals, including man. It is produced by penetrating external radiations and by radioactive compounds given in relatively large single doses (17, 18). The explanation for the "hyperheparinemia" is not entirely clear. *The prolonged clotting time as a result of an increased amount of circulating heparin or heparin-like substance is not specifically a radiation effect.* It has been produced in rabbits by Jacobson, Marks, *et al.* (19*a*, *b*) by exposure to 800 r whole-body roentgen radiation, as well as by the administration of a nitrogen mustard (methyl bis (β-chloroethyl) amine hydrochloride) intracardially in a single dose of 3.0 mg. per kilogram of body weight (Fig. 5) and in man, as reported by Smith, Jacobson, *et al.* (20), when this drug is used therapeutically in the treatment of neoplastic diseases of the blood-forming tissue. *It seems likely, therefore, that "hyperheparinemia" and, thus, a prolonged clotting time may result from any severe acute damage to the hemopoietic system.* The fact that toluidine blue and protamine have been reported by Allen, Bogardus, Jacobson, and Spurr (21) to be effective in temporarily controlling the hemorrhagic manifestations of some cases of acute leukemia, idiopathic thrombocytopenia, and the like, even though no increase in circulating heparin can be unequivocally demonstrated, opens a new approach to research in this field.

It is already evident in our experience on the Plutonium Project that the clotting time may be increased in man as a result of acute over-exposure to penetrating radiations. The work of Prosser, *et al.* (12, 22), Jacobson, *et al.* (23), and Brues, *et al.* (24) indicates that the death of animals after a single exposure to ionizing radiations such as x-rays and fast neutrons is more frequently due to a cumulative effect of derangement in several organ systems than to the failure of a single system such as the hemopoietic system. Thus, for example, death may be due to initial shock within the first twenty-four hours, to overwhelming infection with failure of immune mechanisms, including severe lymphopenia and neutropenia, or to intractable hemorrhage due to hyperheparinemia and thrombocytopenia and increased capillary fragility.

It is of interest to note that, whereas single or repeated exposures in the LD_{50} range may produce a prolonged clotting time due to the increase in circulating heparin or heparin-like substance, *chronic irradiation*, though sufficient to produce panhematopenia and death, produces no apparent change in the blood clotting of animals (25).

(*c*) *Effect of Irradiation on Induced Anemia:* One of the problems facing those charged with the responsibility of the protection of personnel from radiation hazards on the Plutonium Project was whether individuals with a pre-existing anemia would be more adversely affected by externally originating total-body irradiation than individuals with normal values. In an attempt to study this problem, a regenerative anemia was produced in rabbits by the subcutaneous administration of phenylhydrazine hydrochloride or by repeated phlebotomies (26*a*, *b*, *c*, *d*). The hematologic effects of 800 r total-body roentgen irradiation on such anemic animals were compared with those on normal (non-anemic) animals given the same dose. A group of normal untreated and non-irradiated animals was studied simultaneously.

The characteristic initial rise and subsequent reduction in heterophils and immediate precipitous fall in the lymphocyte values followed the administration of 800 r in the group in which a regenerative anemia had been produced, as well as in the irradiated normal animals. The time of recovery of these elements to normal limits in the two groups was likewise comparable. An "abortive rise" in the leukocyte values of both of these groups was noted between

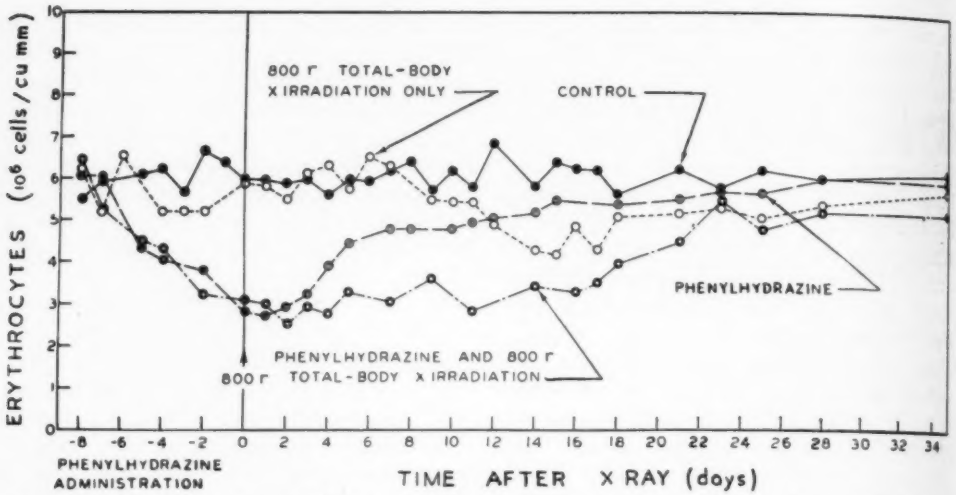

Fig. 6. Effect of a single dose of 800 r whole-body roentgen irradiation on the erythrocyte values in the peripheral blood of normal rabbits and rabbits with a phenylhydrazine-induced anemia. (Originally published in Science **107:** 248, 1948)

the fifth and eleventh day after irradiation.

The group of animals that received roentgen radiation only showed maximum anemia at fourteen days, with recovery by twenty-three days. In the animals in which a regenerative anemia was produced by phenylhydrazine or by bleeding, and which were irradiated at or near the point of maximum anemia, no further anemia developed, and the blood values returned to normal limits by twenty-three days. The phenylhydrazine administration or bleeding was discontinued in these animals two days prior to irradiation. The erythrocyte and hemoglobin values of the group in which an anemia was produced by phenylhydrazine or by phlebotomy, and in which spontaneous recovery was allowed to occur, returned to normal within fourteen days (Fig. 6).

The reticulocyte values of animals that received phenylhydrazine or were bled had reached approximately 27 per cent when radiation was given. This mean value was reduced to a minimum of about 2.0 per cent between three and six days after irradiation and returned to normal limits or higher within twenty-four hours. The mean reticulocyte value of normal control animals that were given 800 r fell maximally within two days, reached a minimum of less than 0.1 per cent, and recovered slowly but completely by twenty-three days (Fig. 4).

The failure of 800 r total-body roentgen irradiation to produce further anemia in animals with a previously induced regenerative anemia or to interfere materially with recovery is dependent in part on the number of surviving primitive erythroblasts in the erythropoietic tissue.

Histologic studies made on animals prepared in a comparable manner and sacrificed at varying intervals indicate that erythropoietic tissue was largely destroyed by seventy-two hours in normal rabbits that were given 800 r, and recovery proceeded slowly. On the other hand, although massive destruction of erythropoietic tissue followed exposure to 800 r in animals in which a regenerative anemia had been produced, the destruction was incomplete and apparently delayed (Fig. 7). These observations appear to indicate that either (1) there may be a delayed response of previously stimulated erythropoietic tissue after exposure to roentgen radiation or (2) actively dividing cells of the erythropoietic series are actually less sensitive to irradiation.

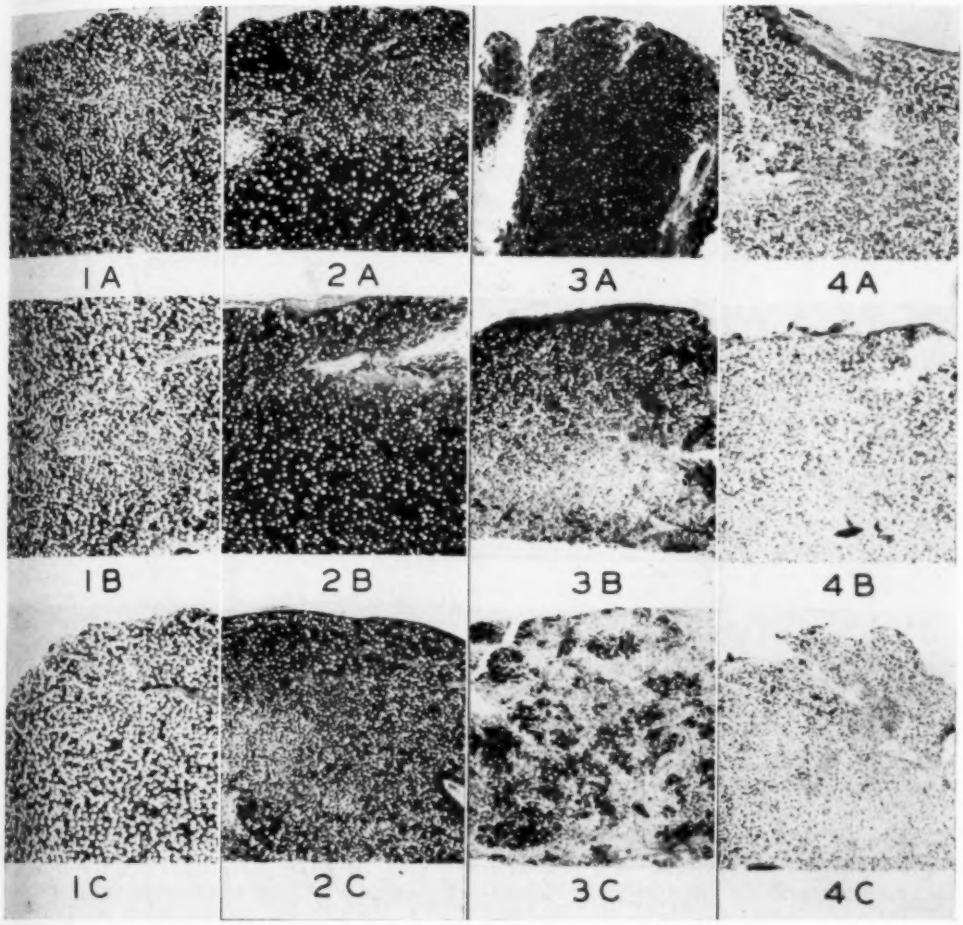

Fig. 7. Hematologic effects of 800 r on normal and hyperplastic bone marrow of the rabbit: 1A, B, C. Range of normal control marrow. 2A, B, C. Bone marrow after phenylhydrazine-induced hyperplasia three, four, and six days, respectively, after phenylhydrazine withdrawal. 3A, B, C. Bone marrow of phenylhydrazine-induced hyperplasia at one, three, and five days, respectively, after 800 r and three, four, and six days, respectively, after phenylhydrazine withdrawal. 4A, B, C. Bone marrow of normal rabbits exposed to 800 r at one, three, and five days after 800 r. ×12 (Originally published in Science **107:** 248, 1948)

Acute Exposure to Fast Neutrons

Although survival data are available on several species of animals exposed to fast neutrons (1, 27), hematologic data in our laboratories are confined to rabbits (23). An exhaustive study was undertaken to obtain quantitative information on the relative biological effectiveness of fast neutrons as compared to x-rays. It must be pointed out that the fast neutron unit used here is an arbitrary unit based on the reading given by the Victoreen ionization chamber when exposed to neutrons.

(*a*) *Dosimetry:* Fast neutron doses were measured with Victoreen condenser r-meters, equipped with 100-r chambers, which were placed within lead shields in cardboard containers between two rabbit boxes or between two tiers of mouse boxes (28). The Victoreen thimble chambers used for the measurement of ionization by fast neutrons had been calibrated in the fast-neutron field of the University of Chicago cyclotron against an instrument of this type first used for this purpose at the Radiation Laboratory of the University of

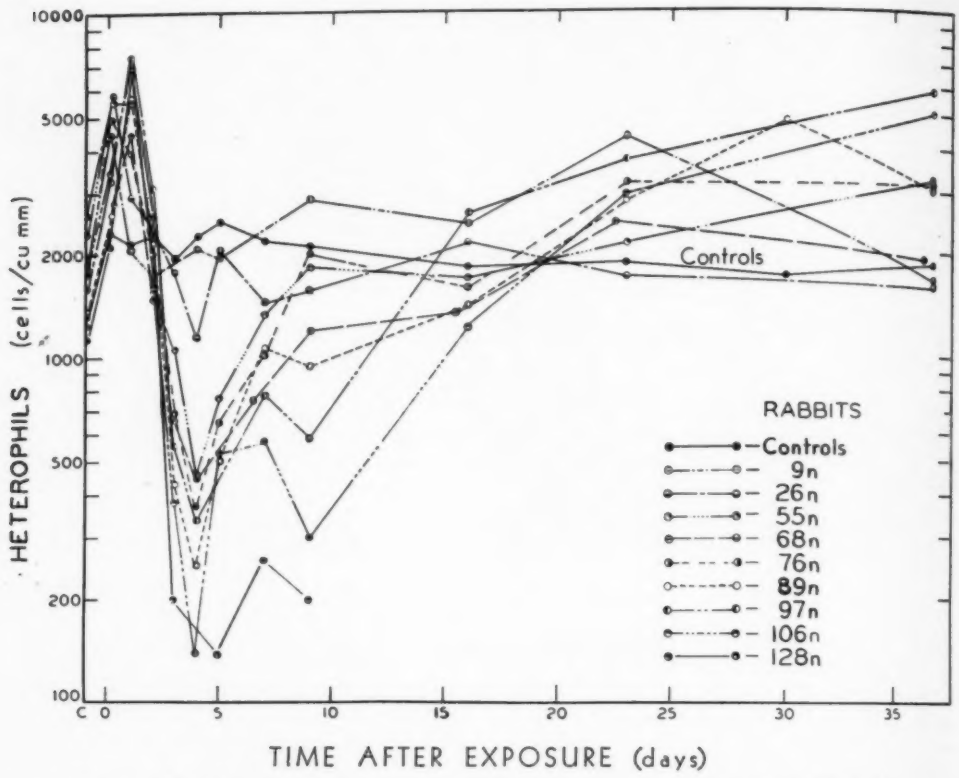

Fig. 8. Effect of exposure to fast neutrons on the heterophils of the peripheral blood of rabbits.

California. Ionization by fast neutrons sufficient to cause a discharge of one division on the r scale of the California instrument has been considered 1 n, the n being a unit of fast neutron dosimetry. Measurement of the ionization by fast neutrons emanating from the Chicago cyclotron should be comparable with determinations made on those emanating from the University of California cyclotron if the same reaction is used.

(*b*) *Probe-Object Distance and Rate of Exposure:* Animals exposed in one set of experiments were approximately 53 cm. from the tip of the probe, and the fast neutrons were administered at a rate of 1 to 6 n per minute. In another group of experiments the animals were approximately 64 cm. from the probe and the rate averaged 0.6 times that at 53 cm. distance.

(*c*) *Effects on Hematological Constituents:* In general, the pattern of effect observed in the peripheral blood of rabbits exposed to fast neutrons from the cyclotron is qualitatively similar to that of x-ray exposure. This is illustrated in Figures 8 and 9.

An initial increase in heterophils followed exposure to fast neutrons in doses of 9 to 128 n. The initial rise occurred within the first twenty-four hours. This was followed, after doses ranging from 26 to 128 n, by a reduction, reaching a minimum in three to five days. No significant reduction in heterophils occurred afer an exposure to 9 n. Recovery to normal limits occurred in all groups exposed to a total dose below 128 n. Animals of the 128-n group expired prior to the sixteenth day after exposure, without apparent recovery.

The number of lymphocytes in the peripheral blood was reduced after the admin-

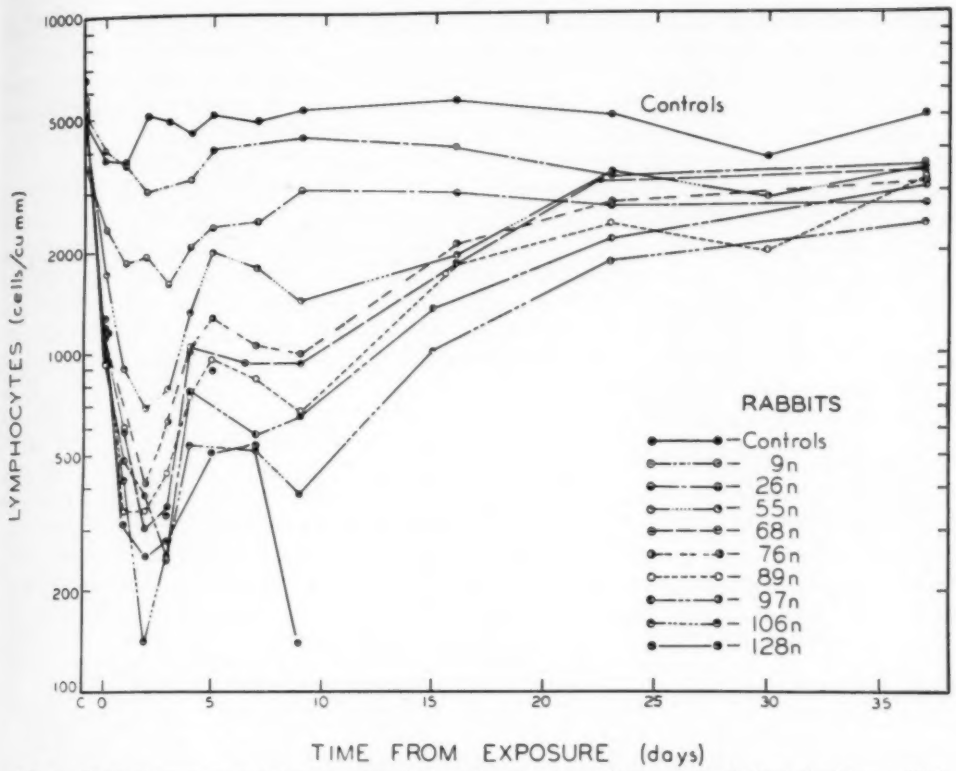

Fig. 9. Effect of exposure to fast neutrons on the lymphocyte values of the peripheral blood of rabbits. With doses of 55 n and above, a temporary elevation in the lymphocyte values occurs between the second and ninth day after exposure.

istration of doses of fast neutrons ranging from 9 to 128 n. This reduction was apparent as early as three hours after exposure, with a maximum reduction at two to three days. Although the lymphocyte values of animals exposed to 9 n were again within the normal control range by five days, the lymphocytes of those animals exposed to 26 n and above had not returned to normal by the thirty-seventh day, when blood counts were discontinued.

A severe normochromic anemia was observed in animals exposed to fast neutrons in the LD_{50} range or above (about 120 n). The maximum anemia in those animals that recovered occurred at about fourteen days, with recovery by twenty-three days. Reticulocytes were reduced to 0.1 per cent or less by the third day in animals exposed to doses of 128 fast neutron units or above.

After doses of 80–89 and 100–108 n, a maximum reduction of approximately 72 per cent in the platelet values of the peripheral blood occurred between the fifth and tenth days, with return to normal values by fifteen and twenty-three days, respectively, in the two exposure levels.

An "abortive rise" in heterophils and lymphocytes occurred after fast neutron exposure and was comparable to that following the exposure of rabbits to x-rays.

The morphologic changes in the cellular constituents of the peripheral blood after fast neutron exposure were identical with those occurring in the peripheral blood of rabbits after "comparable" doses of x-rays.

Pearlman (29) has made a statistical analysis of the hematologic data obtained by Jacobson *et al* (23) from rabbits exposed to x-rays and fast neutrons and has de-

rived a ratio of relative effectiveness of these two radiations. Using the data on the effect of fast neutron and x-ray exposure on the number of circulating heterophils and lymphocytes, he estimated the x/n ratio to be of the order of 6.3. These estimates are in essential agreement with the x/n ratio derived from survival data on rabbits (using the same type of instruments) by Hagen and Zirkle (27). It should be pointed out again that the n unit is arbitrary and that the x/n ratio given does not mean that neutrons are 6.3 times more effective than x-rays in producing the same biological effect.

HEMATOLOGIC EFFECTS OF CHRONIC WHOLE BODY EXPOSURE OF MAMMALS TO EXTERNALLY ORIGINATING RADIATIONS

Prior to the war, no precise experimental information was available on the biological effects of chronic, daily whole-body exposure to penetrating radiations arising externally to the body in the range of the tolerance or "permissible" dose. The penetrating radiations which were of significance on the Plutonium Project were gamma rays, x-rays, and neutrons. In studying these radiations, the animal exposures were given daily for periods of weeks to years. The daily exposure was given in a relatively short period (minutes in one group of experiments), whereas the daily exposure in others was over an eight-hour or twenty-four-hour period.

In the former category (brief daily exposures), the general biological effects of pile radiations (fast neutrons, slow neutrons, and gamma rays) were studied by Zirkle *et al.* (4*b*, 30), Raper *et al.* (31), and Henshaw *et al.* (5, 32). These studies were limited largely to mice. Hematologic studies were not extensive enough in these latter experiments to be of interest in this particular presentation.

Extensive studies of the peripheral blood were carried out by Lorenz *et al.* (33, 34) in a group of experiments involving the chronic exposure of animals (mice, guinea-pigs, and rabbits) to gamma rays. Since experimental irradiation of animals has involved relatively short daily exposures, this more nearly duplicates the type of exposure which is obtained in radiation laboratories and in the clinical practice of radiology and radiotherapy.

Rabbits, Mice, and Guinea-Pigs

The three species studied were rabbits (crosses of Dutch and American Blue), mice (LAF_1 genetically homogeneous hybrids, and strain A), and guinea-pigs (genetically heterogeneous hybrids and inbred strains). The animals were placed in cages that were arranged in a spherical manner about a centrally located radium source. Groups of the three species of animals were exposed to doses of 0.11, 1.1, 2.2, 4.4, or 8.8 r for eight hours per day, and others for twenty-four hours per day, seven days weekly. Although many observations of a biological nature were made on these animals while thus exposed over periods extending beyond three years, only the significant hematological effects will be discussed in this paper. The degree of effect on the hemopoietic organs as reflected in the peripheral blood varied with the species; guinea-pigs were most sensitive, mice intermediate, and rabbits relatively resistant. An equivocal reduction in the total leukocyte count in guinea-pigs on the 0.11 r exposure level and a definite reduction in leukocytes (chiefly lymphocyte reduction) on the 1.1 r exposure level occurred within the first year of exposure. On the other hand, no comparable effects were observed in mice or rabbits exposed on these dose levels. With daily doses of 2.2, 4.4, and 8.8 r, significant hematological effects were eventually apparent in all three species.

Figure 10 illustrates the hematological effects produced by chronic exposure to gamma radiation. As has been universally true in our experiments in which animals were given single whole-body exposures to penetrating radiations, a reduction in the lymphocytes in the peripheral blood was the earliest abnormality noted after chronic radiation exposure. In no instances were absolute increases in lymphocytes, eosino-

phils, or monocytes apparent. A relative increase in lymphocytes was common, however, in animals in which a leukopenia developed in the course of the exposure. Even though a marked lymphopenia or, in fact, an insidious reduction in other hematological values occurred, histologic studies in general failed to show sufficient unequivocal evidence of change in the hemopoietic organs to account for the abnormalities encountered in the peripheral blood.

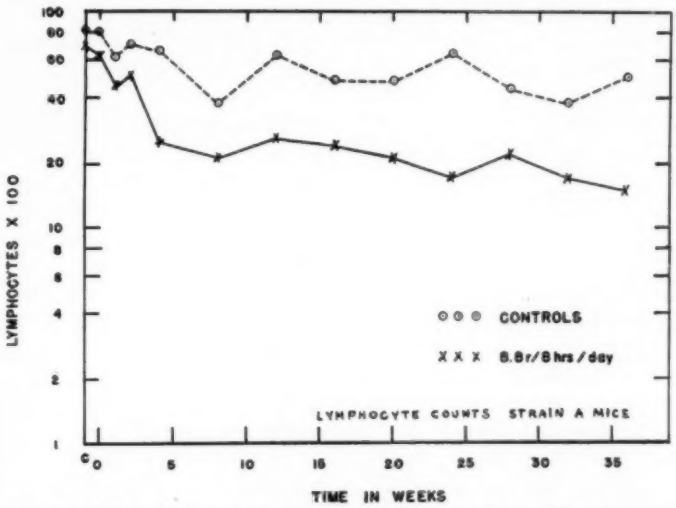

Fig. 10. Effect of an eight-hour daily exposure of mice to 8.8 r (gamma rays) on the lymphocytes of the peripheral blood.

The acute onset of a severe anemia in guinea-pigs on the 2.2, 4.4, and 8.8 r exposure levels was a common cause of death. This observation has been made in animals given whole-body exposure to single doses of x-rays (6) and fast neutrons (23) in the LD_{50} range, as well as in animals given relatively large doses of parenterally administered radioactive elements such as plutonium (35), radium (36), strontium (17), and phosphorus (37). This cannot always be accounted for by hemorrhage or by interruption of erythropoiesis. Schwartz *et al.* (38) have some evidence to indicate that an increased hemolysis may play a role.

A macrocytic anemia appeared in certain of the animals exposed chronically to gamma rays. As is pointed out elsewhere in this report, macrocytic anemias have appeared in animals after exposure to single doses of penetrating radiation and after the parenteral administration of certain radioactive materials. Such anemias occur in man after whole-body exposure to divided doses of roentgen radiation (10, 39) and after P^{32} administration (37). The etiology of the macrocytosis is obscure at the present time. No evidence of associated megaloblastic changes in the bone marrow has been found either by histologic study of erythropoietic tissue or by studying dry smears of bone marrow. That the condition is not due to direct irradiation of the gastro-intestinal tract is brought out by the fact that radioactive elements which localize in blood-forming tissue and not in the gastro-intestinal tract may also produce a marked macrocytosis (35, 36, 37, 17). Jacobson *et al.* (40*a*, *b*) have attempted unsuccessfully to influence the macrocytic anemia by the parenteral administration of folic acid in rats having Sr^{89} intoxication.

Recurrent Anemia After Chronic Exposure to Gamma Radiation

The observation of Lorenz, Jacobson, *et al.* (41) on guinea-pigs exposed to 8.8 r

given in eight hours per day is of interest. If the irradiation of these guinea-pigs was stopped after an anemia as low as 2.5 to 2.8 million erythrocytes per cubic millimeter had developed (total accumulated doses ranging from 800 r to 1,400 r), one of three things happened: (1) in about 50 per cent of the animals further anemia developed and death ensued within a few weeks; (2) approximately 25 per cent of the animals recovered to almost normal limits and have remained normal so far; (3) the blood count of the remaining 25 per cent returned to more or less normal values, remained in the normal range for weeks, and then an anemia recurred or death ensued. This is a most interesting observation deserving further intensive study.

Exposure of Human Beings to Single and Divided Doses of Externally Originating Radiation (Whole-Body Roentgen Radiation)

Few studies have been made on human subjects in which whole-body exposure to single or divided doses of roentgen radiation were used. In those studies that have been reported, the subjects were often so ill as a result of the primary disease when they were treated with x-rays that interpretations of the hematological data were difficult, if not impossible. Low-Beer and Stone (39) undertook treatment of a number of patients with chronic degenerative disease of the joints by whole-body exposure to x-rays. The anterior surface of the patient faced the x-ray tube one treatment day and the posterior surface the next. The dose in roentgens was measured by a thimble chamber on the skin in the center of the field. Thus the doses referred to in Low-Beer and Stone's report are always roentgens on the skin, including back-scatter. All patients except 3 received equal fractional amounts at each treatment. The total doses administered varied from 100 to 300 r given daily in divided doses of 5 to 50 r. The daily treatment required only a relatively few minutes of exposure. Cantril, Jacobson, *et al.* (10) undertook comparable studies. In one group, 8 patients were treated with 400-kv. x-rays, the treatment being given with the patient seated in a light wooden chair with either the right or left side of the body turned toward the x-ray tube. All of the body except the feet was included in the field. The dose was measured by a Victoreen Integron, checked in each instance by determinations with a Victoreen r-meter, using a 25-r ionization chamber. The ionization chamber was placed in the breast pocket of the patient's dressing gown.

Another group was treated with 200-kv. x-rays through somewhat smaller fields. Two fields were used anteriorly and two posteriorly to cover the entire person while lying down. The dose given to each of these fields was considered as the dose to the body. The roentgens per treatment varied from 7 to 100 r. The treatment was given in from two to thirty days. In calculating the dose administered to the patients in this latter group, the amount received by the anterior surface was added to that received by the posterior surface and the sum was designated the "total-body exposure." For example, exposure of each of the anterior and posterior fields to 20 r was interpreted as an exposure of 40 r.

These studies indicated a sensitivity of the hemopoietic system comparable to that in guinea-pigs according to Lorenz *et al.* (33), and comparable to that in dogs according to Prosser and Jacobson (42). With total accumulated doses of 150 r (estimated average dose for the whole body) leukopenia and lymphopenia occurred, the severity of which, however, varied widely from individual to individual. A striking effect was the definite macrocytic anemia that developed in the human subjects in about two hundred days in practically all cases with exposure to total doses of this magnitude. Spontaneous recovery of the hematological constituents of the peripheral blood of these individuals was universal, but the time required for recovery varied widely.

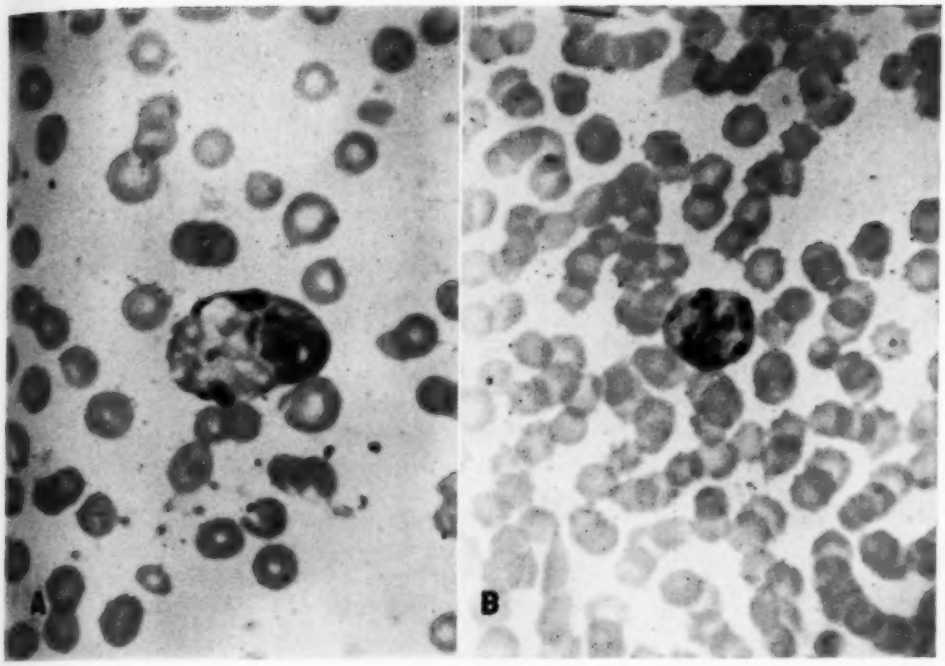

Fig. 11. A. Lymphocyte from the blood of a dog fifteen days after the administration of plutonium, showing nuclear deformities. B. Heterophil from the blood of a rabbit forty-eight hours after 800 r total-body roentgen irradiation, showing nuclear degeneration.

Morphologic Changes in the Cells of the Peripheral Blood Following Acute and Chronic Irradiation

Morphologic changes in the cellular constituents of the peripheral blood of rabbits given whole-body roentgen irradiation parallels the histopathological changes seen in the hemopoietic system (8, 15). After 800 r, and to a lesser extent with doses below this level, nucleated erythrocytes appear in the peripheral blood of the rabbit in increased numbers. The maximum number is not seen in the early period following irradiation but is observed between the tenth and twenty-fifth days. This represents the period of maximum anemia in the peripheral blood and the maximum regeneration in the erythropoietic tissue. The degree of polychromatophilia, poikilocytosis, and anisocytosis depends largely on the type and chronicity of the anemia that is produced in individual animals. Occasionally pyknotic changes were seen in the nucleated red cells; Howell-Jolly bodies were rarely found. Occasionally a few stippled red cells were seen during the stage of anemia. Examination of the reticulocytes stained with brilliant cresyl blue failed to show any change in the morphologic character of the reticulum.

Degenerative morphologic changes in the platelets were found in the peripheral blood of animals following LD_{50} or higher doses of total-body roentgen radiation. Giant platelets were frequently found concomitantly with the reduction in platelet values. Except for increased size and distinctive granular degeneration, no further morphologic alterations were found in the platelets of the peripheral blood. Only on very rare occasions were megakaryocytes found in the peripheral blood after total-body roentgen irradiation in the LD_{50} range.

The morphologic changes in the lymphocytes of the peripheral blood increase with increasing amounts of radiation. Clumping of nuclear chromatin may be seen early. Histologic studies indicate that this change

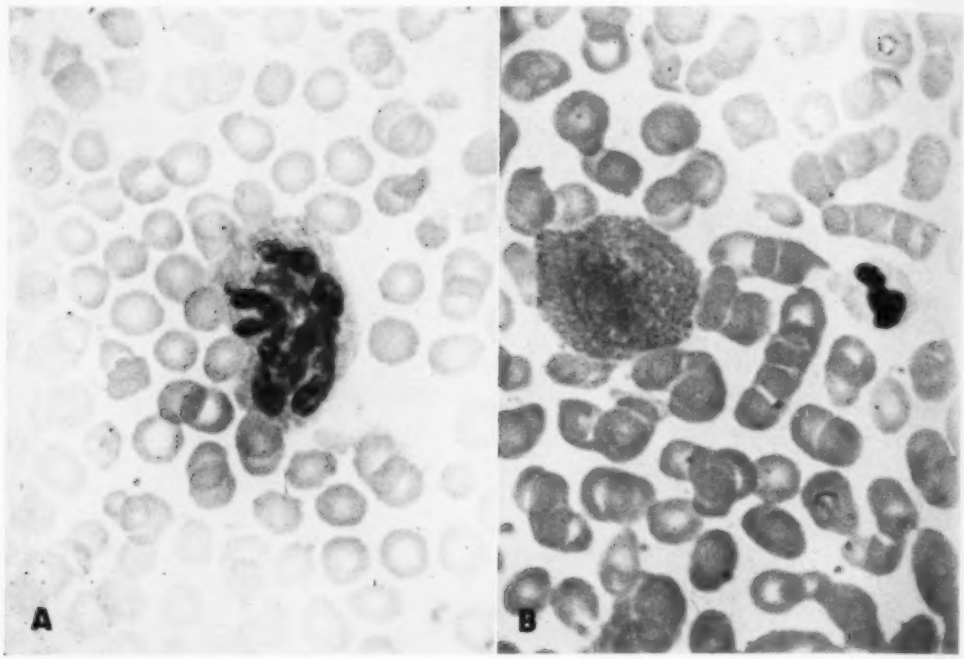

Fig. 12. A. Giant multilobed neutrophil from the blood of a rabbit seventy-two hours after 800 r total-body roentgen irradiation. B. Giant eosinophil from the blood of man eighteen days after the administration of mustard gas.

which occurs with relatively small doses (about 50 r) may actually be reversible in some lymphocytes (8). As it becomes more pronounced, pale bluish opaque areas are encountered. In addition, lymphocytes are seen with rounded chromatin masses seemingly free within the nuclear membrane (Fig. 11*a*). At the time of maximum lymphocyte reduction in the peripheral blood after irradiation, mononuclear cells with a somewhat basophilic cytoplasm and with nucleoli are often prominent. These latter cells are indistinguishable from "blast" forms. Occasionally mitotic "blast" cells appear after semilethal or higher doses. Other lymphocytes appear to have split nuclei and nuclei with considerable fragmentation. With the LD_{50} of acute total-body irradiation, these destructive changes are more pronounced. Remnants of nuclear fragments, without nuclear outline and which cannot be distinguished as belonging to either the myeloid or lymphoid series appear. Many lymphocytes are bilobed, while others are difficult to distinguish from monocytes. During the peak of lymphocyte destruction, phagocytic monocytes with engulfed nuclear debris are found in the peripheral blood smears.

During the phase of rapid reduction of granulocyte values in rabbits, abnormal forms of this series are seen in the peripheral blood. These cells show nuclear deformity and disintegration to the extent that it is impossible to determine at which stage of maturity the cells were damaged (11*b*). The nuclear membrane is destroyed, and in most instances bluish nonspecific granules of uneven contour fill the entire cell, covering the nucleus and cytoplasm to such an extent that it is impossible to identify the cell other than to say it is a damaged or degenerating leukocyte. Other bizarre forms are also seen that are difficult to describe. The cytoplasm of the heterophil may undergo changes following irradiation. Occasionally it contains vac-

nucleus and has a mottled appearance. In some instances, the granules of the heterophils appear to be damaged, since cells are found in which some granules cling to the nuclear membrane while the remainder of the cytoplasm remains clear. Another type of cell seen in rabbits is one that resembles a basket cell but differs from it in having one or two distinct chromatin masses that are deep blue against a network of destroyed perichromatin and cytoplasmic disintegration.

Atypical eosinophils characterized by irregularity in the granules both with regard to size and shape are occasionally seen in the blood smears of dogs following LD_{20} or higher doses of total-body roentgen irradiation. Giant polymorphonuclear leukocytes are frequently seen which appear swollen and contain multilobed nuclei spread over the cytoplasm like globules, having an extremely fine filament branching into eight or more lobes (Fig. 12*a*, *b*).

Morphologic changes in the cellular constituents of the peripheral blood similar to those in animals are found in patients exposed to total-body roentgen irradiation as described in preceding paragraphs. The most consistent morphologic abnormality in the peripheral blood of these patients is the appearance of the atypical basophils described previously. It appears as early as three days after the first exposure, is present in almost every peripheral blood smear throughout treatment, and may be present as long as two and a half months after treatment ceases. Giant multilobed polymorphonuclear cells are frequently seen, and degenerating neutrophils and lymphocytes are found that show the characteristic massing of nuclear chromatin and general disintegration. Occasionally such cells contain round and rod-shaped bodies within the cytoplasm. While they have the appearance of lymphocytes, it is possible that they are atypical and abnormal monocytes containing phagocytized material. Radioactive isotopes, such as plutonium, strontium, and phosphorus, give essentially the same results. As early as four days after treatment, the peripheral blood smears of patients to whom these elements have been administered may contain monocytes with nuclear deformities that show disintegration, lymphocytes with split or bilobed nuclei, and other morphological alterations previously described.

These morphologic changes described above are not specific for radiation, since they are likewise produced with the administration of nitrogen mustards (37, 43, 44).

COMPARATIVE EFFECTS OF PARENTERALLY AND ORALLY ADMINISTERED RADIOACTIVE ELEMENTS (ACUTE AND CHRONIC STUDIES)

The general biological effects of the various radioelements produced by fission have been fully described elsewhere by Brues *et al.* (45*a*, *b*), Lisco *et al.* (46), Bloom *et al.* (8, 47), Prosser *et al* (22, 48), and Jacobson *et al.* (17, 18, 35, 36). As was recently pointed out by Jacobson and Marks (49), however, the degree of effect produced by the radioelements on blood and blood-forming tissue is dependent on the size of the dose administered and the extent of localization in or adjacent to blood-forming tissue. With all the radioelements that we have studied thus far, whether they were localized in bone or more generally distributed in the body, a reduction in the lymphocyte values of the peripheral blood is the most sensitive indicator of *acute* or *subacute* effects. Lymphocyte reduction may occur in the absence of histologic evidence of radiation damage to lymphatic tissue. The dose of radioactive elements, such as Sr^{89} and radium, required to produce bone sarcomas, lymphomas, and the like (46, 50), is practically identical with that required to produce perceptible mean reduction of the leukocytes of the peripheral blood.

Plutonium: Pu^{239}, which has a half-life of 2.4×10^4 years, is an alpha emitter that localizes largely in bone but also, to a lesser extent, in the liver when given subcutaneously or intravenously. Hematologic studies of the peripheral blood after the administration of plutonium as citrate have

been made on mice, rats, and rabbits (35). Intravenous and intracardial doses of 0.001 to 0.119 microcurie[7] per gram of body weight have been given to rabbits; and intravenous and intramuscular doses of 0.003 to 0.125 microcurie per gram of body weight have been given to the rat. There appeared to be no significant species difference in the sensitivity of the hemopoietic system of the mouse, rat, and rabbit to plutonium on the basis of the above experiments, nor was there any apparent strain difference within a species, or sex difference within a strain. No significant hematologic change in the peripheral blood occurred after intracardial, intravenous, or intramuscular injection of 0.0003 or 0.0006 microcurie per gram of body weight of plutonium in the mouse, rat, or rabbit during approximately three hundred days of observation. A dose in the range of 0.003 microcurie per gram of body weight, however, produced a minimum to moderate depression of the leukocytes and platelets in the three species within the first one hundred days. A dose of 0.0063 microcurie per gram of body weight produced a moderate to severe and sustained leukopenia in all three species and caused an anemia in mice and rats. This latter dose caused early death in rats and mice (135 days). Doses above 0.0063 microcurie per gram of body weight produced correspondingly more severe and sustained anemia, leukopenia, reticulocyte reduction, and platelet reduction in mice and rats.

A macrocytosis, as evidenced by an increased mean erythrocyte diameter and increased mean corpuscular hemoglobin, became apparent in rats after the parenteral administration of doses of plutonium between 0.0063 and 0.063 microcurie per gram of body weight. This effect was less significant in mice and rabbits after comparable doses. The acute and subacute cellular changes seen in the peripheral blood following plutonium administration were paralleled by concomitant histologic changes in the hemopoietic tissue.

[7] 1 microcurie = 3.7×10^4 disintegrations per second.

The fact that effects on the hemopoietic system may be reflected in the peripheral blood of plutonium-injected animals while comparable doses of injected radium produce no such blood change and yet give rise to bone tumors earlier and in greater number, may be related to the difference in the site of deposition of the two elements. In general, the peripheral blood fails to reflect the development of bone sarcoma in radium-injected animals. The development of an increase in mean corpuscular hemoglobin and erythrocyte cell size independent of reticulocyte increase or decrease seems to be characteristic of plutonium when given parenterally within certain dose limits. It is likely that other internally deposited elements which affect the hemopoietic system will act likewise if chronically administered within certain dose limits. The greatest degree of macrocytosis thus far encountered in the experimental animal has been in the rat (17, 40*a*) and goat (51) after radiostrontium (Sr^{89}) administration.

Radium: The biologic effect of radium, which has a half-life of 1,590 years, is mainly due to alpha radiation. This element localizes in bone as do plutonium and radiostrontium. Hematologic studies (36) of the peripheral blood of rats, mice, and rabbits after the intraperitoneal, intravenous, or intracardial injection of radium chloride indicate the following:

1. There appeared to be no significant species difference in the sensitivity of the hemopoietic systems of the rat and mouse to radium chloride, but rabbits were slightly more resistant than these species. CF-1 female mice[8] appeared to be somewhat more resistant than Strain A male mice.[9] This may represent either a sex or strain difference.

2. Doses of 0.01 microgram or lower caused no detectable hematologic alterations in the peripheral blood of rats, mice, or rabbits. Doses in the range of 0.02 to

[8] CF-1 raised by Carworth Farms. Homozygous for the recessive genes aa bb cc.

[9] A back cross, Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. Heterogeneous stock.

0.03 microgram resulted in anemias and leukocyte reductions in rats and ABC male mice.

Doses as high as 0.1 microgram, however, failed to produce an anemia in the rabbit, but did cause a reduction in leukocytes. A dose of 0.94 microgram in the rat resulted in reticulocyte and platelet reduction.

3. Radium intoxication produced morphologic changes in the nucleated cells of the peripheral blood comparable to those that occur after exposure to external radiations and parenterally administered plutonium.

4. A macrocytic anemia developed in rats, mice, and rabbits following the parenteral administration of radium chloride in doses between 0.1 and 0.2 microgram.

Yttrium (Y^{91}): Radioactive yttrium (Y^{91}) was administered by gavage to a group of rats in single doses of 5, 10 and 20 microcuries (52) in an attempt to determine the effect of beta radiation on the gastro-intestinal tract. This element, which is a beta emitter and which has a half-life of fifty-seven days, was given as the chloride. Absorption from the gastro-intestinal tract was negligible. In another group of animals, daily gavages of from 0.3 to 2.0 microcuries were continued up to one-hundred and seventy-eight days. A single dose of 20 microcuries produced a marked initial elevation in the erythrocyte and hemoglobin values, followed by a severe anemia that reached its maximum at twenty days. A 75 per cent reduction in lymphocytes occurred within three days, but the lymphocyte count reached a normal value by thirty-five days. The heterophil values after this dose were extremely erratic. A dose of 10 microcuries produced a temporary lymphopenia and only an erratic heterophilia. No hematologic effect was observed after single doses of less than 10 microcuries.

Daily gavage of yttrium^{91} in amounts from 0.3 to 2.0 microcuries produced no anemia. A sustained heterophilia was present in all groups receiving daily gavage. In one of the experiments, a moderate lymphopenia was produced by the daily gavage of 0.3 and 1.0 microcurie which reached its maximum at sixty days, but gradual recovery to normal values occurred by ninety days, even though yttrium administration was continued through one-hundred and seventy-eight days. In another experiment, daily ingestion of 0.3, 1.0, and 2.0 microcuries produced a lymphopenia that reached its maximum degree at ninety days. Upon discontinuation of yttrium^{91} by gavage at ninety days, a prompt return of the lymphocyte values to normal levels occurred. It is suggested that the lymphopenia described above results from the local effects of beta irradiation on the lymphoid tissue of the gastro-intestinal tract.

No significant morphologic change in the nucleated cells or erythrocytes occurred after single or repeated doses of ingested yttrium^{91}.

Sodium (Na^{24}): Groups of Strain A back-cross and CF-1 male mice were injected intraperitoneally with sodium^{24} as the chloride in doses of 12, 23, 24, 48, 75, or 95 microcuries (53). This element, which has a half-life of 14.8 hours, is a beta and gamma emitter. Administered intraperitoneally it is distributed uniformly throughout the body. Leukocyte counts and differential blood smears were made on all animals before the injection of the radioactive sodium and at intervals thereafter through ten days in one experiment and through fifteen days in another. A moderate to severe leukopenia followed the injection of all the above doses except 12 microcuries. Death of the animals that received 48, 75, and 95 microcuries occurred before the eighth day. The neutrophils rose slightly by three days in the group that received 95 microcuries. No further sampling was possible in this group because of the death of all the animals. No reduction of neutrophils followed the injection of 25 microcuries per gram in one experiment, while 23, 48, and 74 microcuries produced a marked neutropenia in another experiment. Lymphopenia occurred in all groups of animals that received

23, 24, 48, 74, and 95 microcuries and remained thus depressed until death of the animals or until sampling was discontinued.

Barium-Lanthanum (*Ba-La*)^{140}: These two radio-isotopes are considered together because the disintegration of barium (Ba^{140}) forms a short-lived lanthanum daughter (La^{140}). Ba^{140} has a half-life of twelve and a half days and La^{140} has a half-life of forty hours. Barium^{140} and lanthanum^{140} emit a beta and a gamma ray. The radiation effects of these two isotopes in the mouse, however, may be entirely attributed to the beta rays (54). (Barium-lanthanum)^{140} administered intraperitoneally to mice as the chloride in a dose of 0.2 microcurie produced a decrease of low significance in the leukocytes, lymphocytes, and heterophils during the twenty-nine days of observation (55). A dose of 1.9 microcuries produced in these constituents a significant and rapid reduction that was sustained for approximately sixty days. Rapid reduction in these values and death within fifteen days followed the administration of 17 microcuries. No significant change occurred in erythrocyte or hemoglobin values with these doses during the sixty days of observation.

Strontium (Sr^{89}): This element, which emits beta rays only, has a half-life of fifty-five days and like radium and plutonium localizes in bone. Hematologic studies of the peripheral blood of rabbits, rats, and mice after the intraperitoneal or stomach tube administration of Sr^{89} chloride in doses from 0.015 to 14.5 microcuries for varying periods up to one hundred and eight weeks indicated that reductions in the heterophil and in the lymphocyte values were about equally sensitive indicators of acute and subacute effects (17). Moderate but significant reduction in heterophil values followed the intraperitoneal injection of 0.068 microcurie in Strain A back-cross male mice; no effect was apparent after the administration of 0.015 microcurie by the same route in Strain A back-cross males and Carworth females. Progressively more significant and sustained reduction in heterophil and lymphocyte values followed higher doses. No anemia occurred in mice given doses of 0.034 microcurie or lower, but a moderate anemia was apparent with a dose of approximately 2.0 microcuries in this species. The minimal dose exerting a mean detectable reduction in heterophil values in rats was between 0.22 and 0.25 microcurie. Doses above this amount produced a progressively more severe heterophil depression and lymphopenia. Stomach tube administration of the isotope was studied in rats for comparison with doses given by the intraperitoneal route. The intraperitoneal dose required to produce a comparable effect on the cellular constituents of the peripheral blood is approximately twice that required by stomach tube. An intraperitoneal dose of 1.0 microcurie produced a significant reduction of heterophil values in the rabbit. Following an intraperitoneal dose of 3.0 microcuries a significant reduction in hemoglobin and erythrocyte values occurred, with a rapid recovery. A sustained heterophil and lymphocyte reduction of significance was also apparent after this dose.

Although drastic depletion of hemopoiesis in the bone marrow follows Sr^{89} intoxication, no anemia developed in mice with doses up to 2.0 microcuries per gram due to the rapid development of extramedullary erythropoiesis in the spleen. Jacobson, Simmons, *et al.* (56) have shown that this dose produced a severe anemia in splenectomized animals (Fig. 13).

We have also studied the effect of Sr^{89} on dogs and goats (48, 51). The minimum effective dose required to produce hematologic effects in these animals has not been determined. The lowest dose given to dogs was 0.10 microcurie per gram (intramuscularly). Four days after this dose, the leukocytes were reduced approximately 60 per cent. The dogs showed no clinical symptoms, however, and all survived. The approximate LD_{50} range for dogs and goats is 1.0 microcurie per gram. The most spectacular macrocytosis yet encountered in animals made anemic by exposure to external penetrating radiations or paren-

teral administration of radioelements was seen in rats (17) and goats (51) given Sr^{89}.

SO-CALLED STIMULATING EFFECTS OF RADIATION ON HEMOPOIESIS

The idea that small doses of radiation "stimulate" cellular activity and cellular multiplication is not correct (57). In many of the experiments described above the hematologic effects of radiations applied acutely or chronically in relatively large to small doses were carefully studied with this consideration in mind. In no instance was primary stimulation detected. On the other hand, compensatory increases were not infrequently encountered after initial depressions of the various cellular constituents of the peripheral blood. This is in agreement with the work of Murphy (58), who has often been misquoted. After acute total-body exposure to penetrating x-rays and fast neutrons in the LD_{50} range, a marked initial increase in heterophils occurs in rabbits within the first twenty-four hours without a preceding depression. (A subsequent marked reduction occurs.) This heterophil increase has been interpreted by Isaacs (59) to represent a hastened maturation of the myeloid precursors and may represent a "stimulation." Low-Beer and Stone (39) reported a marked monocytosis in patients with chronic degenerative arthritis after total-body irradiation with divided doses of penentrating x-rays totalling up to 300 r. This phenomenon did not occur in patients similarly treated by Cantril, Jacobson *et al.* (10), but the underlying disease was not the same. It seems likely that the monocytosis was due to an altered reaction to radiation related to the underlying disease and not a primary stimulation of monocyte production.

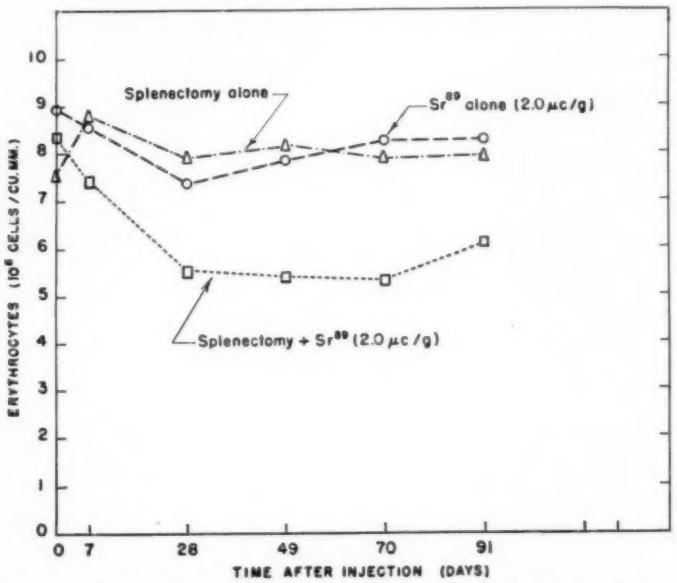

Fig. 13. Erythrocyte values of normal and splenectomized rats injected with a single dose of strontium[89], 2.0 microcuries per gram.

STUDIES ON THE PERIPHERAL BLOOD OF PLUTONIUM PROJECT PERSONNEL EXPOSED OR POTENTIALLY EXPOSED TO RADIATIONS

As reported by Jacobson and Marks (60), an extensive study of the hematologic constituents of the peripheral blood of Plutonium Project personnel was carried on. This was done in an attempt to dis-

cover evidence of incipient injury to personnel from radiation exposure. All employees accepted for employment were classified in terms of individual occupation hazard in one of two groups: (1) the control group, and (2) the work-hazard group. The control group consisted of all employees working in areas in which exposure to radiations was negligible or absent. The work-hazard group consisted of all individuals in the laboratory who were exposed or potentially exposed to physically hazardous materials. The frequency of the hematologic examinations that were conducted in these two groups varied from daily studies to studies conducted every three months.

Relatively few instances were encountered in which changes in the hematologic constituents of the peripheral blood of personnel could be attributed to contact with external radiation or the deposition of radioactive materials within the body. The great variation in the steady state of the various hematologic constituents of the peripheral blood from one individual to another, the inaccuracy of modern methods for measuring these constituents, and the individual physiological variation from hour to hour, day to day, and month to month made it almost impossible to interpret minor fluctuations possibly resulting from acute or chronic radiation exposure.

However, statistical analysis by Pearlman and Sacher (61) indicated that the mean levels of several blood elements on personnel working in the presence of radiation or metal hazards at the end of six months and one year of employment showed no significant decrease. A slight increase in mean lymphocyte values in the groups exposed to radiation hazards and those of the metal-working groups was on the borderline of significance ($p = 0.05$). Individual daily monitoring indicated that the average measured exposure is less than 0.1 r per day for all individuals in these groups. More emphasis on basic biological research on the mechanism of action of ionizing radiations is obviously required before one can logically devise clinically applicable tests to determine and evaluate incipient damage from these agents. The concept that no amount of ionizing radiation can be tolerated by man obviously cannot be accepted if work is to continue in this field, but it is important that a firm biological basis for a permissible dose be established.

NOTE: The authors wish to acknowledge the cooperation of Drs. Kenneth S. Cole, Robert S. Stone, and Raymond E. Zirkle.

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SUMARIO

Los Efectos Hematológicos de las Radiaciones Yonizantes

Esta minuciosa comunicación versa sobre los efectos hematológicos de la exposición aguda y crónica de todo el cuerpo a los rayos X y los neutrones veloces. Para ambas formas de irradiación y ambas formas de exposición, el indicador más sensible del efecto de la irradiación susceptible de reconocimiento en la sangre periférica de los animales de experimentación estudiados, consistió en una disminución total del número de linfocitos por milímetro cúbico. Las grandes dosis aisladas de rayos X produjeron anemia en los animales normales, en tanto que no se evocó más anemia en los que ya tenían una anemia previamente provocada con fenilhidracina. Los estudios histopatológicos coincidentes con esta última observación indicaron que, en contraposición a la creencia general, los eritroblastos más inmaduros eran menos sensibles a la irradiación que los precursores más maduros. En cierto número de los animales expuestos crónicamente a los rayos gamma apareció una anemia macrocitaria, y Low-Beer y Stone pasan por haber observado una anemia macrocitaria bien definida en sujetos humanos que recibían la radioterapia en todo el cuerpo, unos 200 días después de recibir dosis totales acumuladas de 150 r, habiendo por fin reposiciones espontáneas en todos los casos.

Las dosis letales o semiletales ya de rayos X o de neutrones veloces produjeron una prolongación significativa del tiempo de coagulación de la sangre íntegra de animales y seres humanos. Esta anomalía de la coagulación fué considerada como efecto de un aumento de la heparina o de una sustancia heparinoidea, dado que podía hacerse virar a lo normal el tiempo de coagulación mediante la inyección endovenosa de sustancias antiheparínicas específicas, tales como el azul de toluidina o el sulfato de protamina.

Las alteraciones morfológicas en las células de la sangre periférica de los conejos que recibieron la irradiación roentgen en todo el cuerpo se conformaron a la histopatología observada en el aparato hematopoyético. Tras dosis de 800 r aparecieron en la sangre periférica cantidades crecientes de eritrocitos nucleares, alcanzando su máximo en un plazo de diez a veinticinco días, lo cual representa el período de anemia máxima de la sangre periférica y de regeneración máxima del tejido eritropoyético. Las alteraciones morfológicas de los linfocitos de la sangre periférica aumentaron al acrecentarse las dosis de rayos. Para la epoca de linfopenia máxima, a menudo sobresalían los mononucleares con un citoplasma algo basófilo y con nucléolos. Algunos linfocitos tenían aparentemente núcleos hendidos o muy fragmentados. Estas y otras alteraciones morfológicas también se observan en los enfermos expuestos a la roentgenoterapia total del cuerpo, siendo el hallazgo más constante la aparición de glóbulos con degeneración basófila. Estas alteraciones no son específicas para la irradiación, pues se observan también después de la administración de las mostazas de nitrogeno.

Lo mismo que sucedió con la irradiación externa, la disminución de los valores linfocitarios de la sangre periférica resultó ser el indicador más sensible de los efectos agudos o subagudos producidos por la administración parentérica y oral de elementos radioactivos (plutonio, radio, itrio, sodio, estroncio, etc.), ya localizados en los huesos o distribuídos más generalmente por el cuerpo.

En ningún caso se observó la menor excitación primaria de la actividad y multiplicación celulares a continuación de dosis grandes o pequeñas de irradiación, aunque no fueron raros los aumentos compensadores consecutivos a bajas iniciales de los various componentes celulares de la sangre periférica.

Los exámenes hematológicos del personal dedicado a trabajos en "Plutonio" revelaron relativamente pocos casos en los que pudieran imputarse alteraciones de la sangre periférica al contacto con la irradiación externa o al depósito de sustancias radioactivas en el cuerpo.

The Lethal Dose of Total-Body X-Ray Irradiation in Swine[1,2]

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THE DEVELOPMENT of the atomic bomb has stimulated great interest in the study of ionizing radiation injury to living tissue. A large field experiment, designed to determine both physical and biological effects of the release of atomic energy, was successfully carried out by Joint Task Force One in Operation Crossroads in the summer of 1946 (1, 2). It is desirable to produce comparable ionizing radiation lesions in laboratory experiments not only to allow correlation with and better understanding of the data obtained at Bikini, but also to serve as a basis for future studies of ionizing radiation injuries. Previous work has largely concerned smaller forms. Some interest lies in studying larger animals, such as swine, not only from the standpoint of greater tissue masses and the increasing significance of depth dosage, but also because of a possible closer relation to the radiosensitivity of man.

Groups of swine were given known amounts of total body irradiation with hard x-rays emanating from an industrial x-ray tube under as nearly identical conditions as possible. This report concerns the first phase of the laboratory studies, namely, the amount of radiation administered to the whole body (to each lateral aspect in succession) necessary to kill, during a period of 30 days, 50 per cent of the animals exposed (LD 50/30). Subsequent reports will describe the pathologic and hematologic findings.

MATERIALS AND METHODS

The x-ray generator used was a 1,000-kv., 3-ma. General Electric Industrial x-ray unit which produced both a transmitted and an angular beam. Due to the limited area covered by the transmitted beam, it was blocked off with lead plates, and the animals were exposed to radiations from the angular beam only (Fig. 1). At a given elevation the angular beam produced radiations of similar quality and quantity in an arc of 360° around the tube. In order to obtain maximum efficiency and to avoid large differences in doses in different parts of the horizontal area occupied by the animals during the test, only that portion of the angular beam was used that fell between 95 and 135° from the vertical (Figs. 1 and 2).

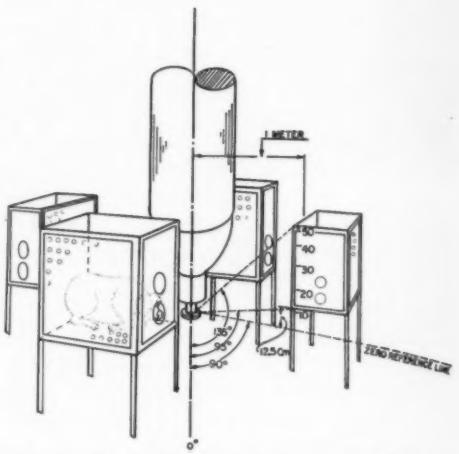

Fig. 1. The 1,000-kv. unit with animal cages in place for exposure to that portion of the angular beam between 95 and 135°.

The x-ray unit was calibrated to determine the output and depth dose of the beam. Throughout the experiment a constant output was maintained. The output

[1] From the Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. Accepted for publication in February 1948. [2] The opinions expressed in this report are those of the authors and are not necessarily those of the Navy Department.

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of the beam was measured at each of the four animal stations vertically from zero reference (90° from vertical) at 10, 20, 30, 40, and 50 cm., the zero reference being used for the one meter distance (Fig. 1). The output at these points varied from approximately 27 r/min. at the 10 and 50 cm. points to 33 r/min. at the 30 cm. point. From these measurements, it was determined that an average output of 30 r/min. was delivered at 1,000 kv., 3 ma., with no added filter, at 1 meter distance, with the bottom of the cages at 12.5 cm. above zero reference. These measurements were accomplished before the experiment was begun, and a check was made at one of the animal positions (selected in rotation) each day before exposure.

The time of exposure to irradiation at 30 r per minute varied from 13.3 minutes in the 200-r group to 40 minutes in the 600 r group. At the mid-point of the exposure period a short interval, not exceeding five minutes, was required to rearrange the animals for exposure of the opposite lateral aspect. Thus the maximum time from beginning to end of exposure to radiation in this experiment (600-r group) was 45 minutes.

The depth dose of the angular beam used was determined in a phantom of 63 per cent rice and 37 per cent sodium bicarbonate in a 37-cm. cube (3).

Measurements were made at four depths at each of five elevations (10, 20, 30, 40, 50 cm.). The five elevations measured were distributed among the four animal locations. From these measurements the following average depth doses were calculated:

Depth in cm.	Per Cent of r Delivered in Air
3.5	108.5
12.5	50.0
24.5	17.0
36.5	5.5

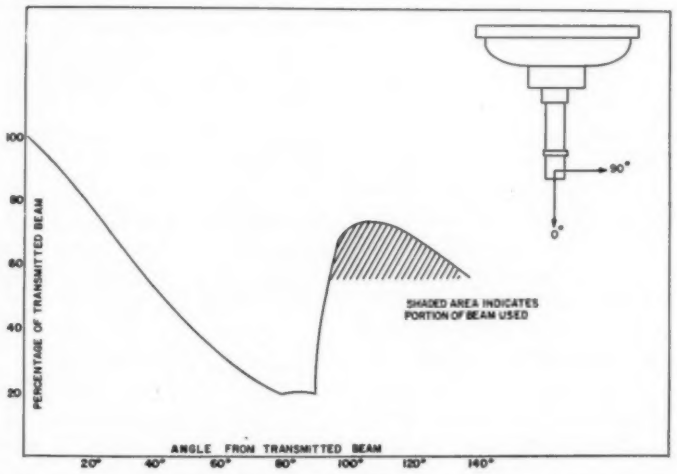

Fig. 2. X-ray distribution curve of 1,000-kv.p. unit modified from General Electric Corporation chart of Aug. 27, 1943.

Recently calibrated Victoreen condenser chambers of 25 r, 100 r, and 250 r capacities were used for calibrating the machine. Data obtained by Quimby and Focht (4) have shown properly calibrated Victoreen chambers of 25 r and 100 r capacities to be accurate within 2 per cent in calibrating 1,000-kv. radiation. The 250-r chamber gave consistently higher readings than the 25-r and 100-r chambers for a given exposure, and a correction factor was therefore used with this largest chamber.

The variation in animal sizes presented a problem. For the 200-r group, for instance, the animals at the time of the experiment

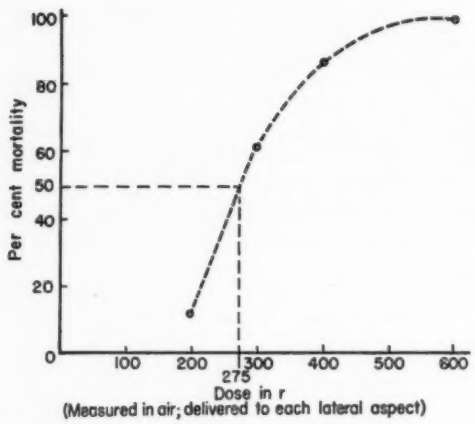

Fig. 3. Effect of amount of radiation on 30-day mortality rate in swine.

weighed 119, 123, 145, 158, 176, 189, 202, and 240 pounds. In the other groups only random weights were taken, but differences of 50 to 100 pounds in weight were the rule. To compensate for the weight differences and to achieve as uniform a thickness of the animals as possible, they were irradiated while confined in the prone position in quarter-inch "Presdwood" cages measuring 27.9 cm. in width and 113 cm. in length. The sides of the animals touched or were compressed by the sides of the cages.

Since the thickness of the animals was approximately twice the 50 per cent depth dose as measured by the phantom described above, the animals were given the same dose on both lateral aspects of the body. This procedure was employed in order to achieve more uniform distribution of the dose to the entire thickness of the animal.

The error introduced by placing the animals tangential to the circular beam at one meter radius was an additional factor. Thus an animal 100 cm. long would have received 20 per cent less radiation at each end than at the mid point.

The animals employed in these studies were sexually mature, well nourished swine about twelve to fifteen months old. There were 4 males and 4 females in each exposure group. They were herd mates, bred from mixed Chester White-Poland China-Duroc Jersey stock. From the third through the seventh month of life the pigs were maintained on a low-caloric diet, consisting of 90 per cent rolled oats, 10 per cent tankage, with salt and alfalfa hay *ad libitum*. They were then put on a mixed grain-tankage-mineral-high-vitamin-high-caloric diet recommended by Mr. John H. Zeller of the U. S. Department of Agriculture. They were fed and watered in the morning before exposure in the afternoon. All animals were vigorous and in good health at time of exposure.

RESULTS

Within a 30-day period following exposure, animals died from the effects of irradiation in the proportions of 1 of 8 (12.5 per cent) that received 200 r, 5 of 8 (62.5 per cent) that received 300 r, 7 of 8 (87.5 per cent) that received 400 r, and 8 of 8 (100 per cent) that received 600 r. All doses were measured in air and were delivered to each lateral aspect of the body in succession. The mortality data when plotted as a function of dose appear to give an "S"-shaped curve (Fig. 3) similar to those obtained by Ellinger (5) on mice and guinea-pigs. From this curve the LD 50/30 is evidently about 275 r administered bilaterally.

One of the 3 animals in the 300-r group that survived the 30-day period died on the ninety-first day following irradiation. This animal had had a persistently low white blood cell count following irradiation,[7] but was beginning to show evidence of recovery when pneumonia developed and death ensued. Since presumably the leukopenia and lowered resistance to infection were the direct results of irradiation, this death may be considered as a delayed one due to radiation.

The relationship of dose, sex, survival time, and total mortality is brought out in Figure 4. The percentage of deaths was lower in the lower dose ranges and increased as the dose increased. At 600 r all animals succumbed.

[7] Details will be published in a forthcoming report devoted to hematologic changes in irradiated animals.

There is not sufficient evidence to demonstrate the influence of sex *per se* on the reaction to irradiation.

Individual variation in resistance to irradiation appeared in the lower dose ranges where animals survived for markedly different lengths of time. This was less evident in the higher dose ranges, although two animals, one at 400 r and one at 600 r, survived for several days longer than the others in their respective groups (Fig. 4).

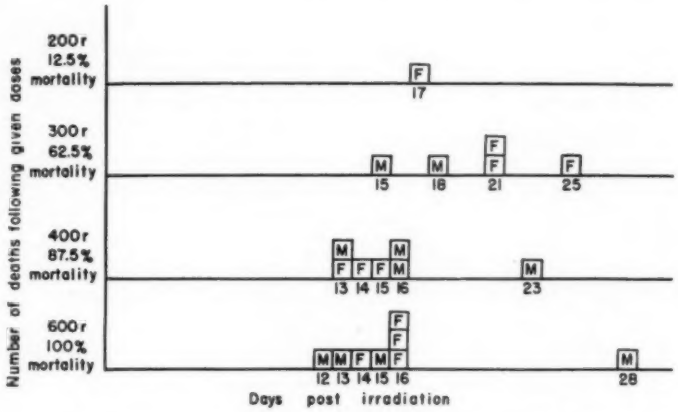

Fig. 4. The time-dose-sex-mortality relationship in swine (4 males and 4 females in each experiment) exposed to ionizing radiations at 1 meter distance from a 1,000-kv., 3-ma. source. The dose was measured in air and delivered to each lateral aspect of the animal.

DISCUSSION

The variance of the output of the x-ray beam at different levels above the horizontal zero reference and the variation of the weight and habitus of the experimental animals were the greatest variables encountered.

Because of the distinct differences in technic utilized by various investigators, it is not possible to compare the interpolated LD 50/30 in swine with the lethal dose studies in other animals as described by Ellinger (5), Prosser *et al.* (6), and others. It is of interest to note, however, that the 30-day mortality data plotted as a function of bilaterally administered dose fell on an "S"-shaped curve considered typical of lethal dose studies in much larger series. It is felt that this points to the validity of the results in this small group.

It has not appeared feasible to attempt an evaluation of density differences within the same animal or to apply correction factors for these.

The experimental apparatus utilized was chosen to give as close an approach to atomic bomb radiation as practicable. It is obvious, however, that the time required for delivery of the dose, the total r dose, and the character of the radiation differed considerably from corresponding factors that pertained in the test Able atomic bomb explosion at Bikini. These differences, however, do not preclude a common basis for comparison.

In this study the maximum time between the onset and conclusion of irradiation was 45 minutes (600 r administered bilaterally). While the exposure time exceeded by far the extremely short duration of the radiation delivered by the atomic bomb, the time was probably not prolonged sufficiently to permit appreciable recovery of the animals during the period of exposure. The total r dose and the character of radiation employed were satisfactory to determine the LD 50/30. In spite of differences between the several ionizing radiation components of the atomic bomb and

1,000-kv. x-rays alone, the biologic response to roentgen equivalent amounts is considered to be essentially similar (6, 7, 8). It is believed, therefore, that certain aspects of the two studies may reasonably be compared.

SUMMARY AND CONCLUSIONS

1. Adult, healthy, hybrid swine were exposed in groups of 8 (4 males and 4 females) to predetermined amounts of total-body radiation delivered in succession to each lateral aspect of the body one meter from a 1,000 kv., 3-ma. x-ray source.

2. The 30-day per cent mortality plotted as a function of the bilaterally administered dose gave an "S"-shaped curve, the LD 50/30 of which was taken by interpolation to be 275 r.

ACKNOWLEDGMENTS: The co-operation of Capt. C. F. Behrens, MC, USN, the Biophysics Section of the National Cancer Institute, The Therapy Department of the Army Medical Center, and the Materials Testing Laboratory of the Naval Gun Factory, Washington, D. C., is gratefully acknowledged.

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SUMARIO

La Dosis Letal de Irradiación Total del Cuerpo con Rayos X en el Cerdo

Cerdos híbridos, adultos, sanos fueron expuestos en grupos de 8 (4 machos y 4 hembras) a dosis predeterminadas de irradiación total del cuerpo, entregadas sucesivamente a cada cara lateral del cuerpo a un metro de un foco de rayos X, de 1,000 kv. y 3 ma.

La mortalidad porcentaria de 30 días, trazada como función de la dosis administrada bilateralmente, dió una curva en S. La dosis necesaria para matar, durante un período de 30 días, 50 por ciento de los animales (DL/50/30) fué computada por interpolación en 275 r.

Aberrant Tissue Developments in Rats Exposed to Beta Rays

The Late Effects of P^{32} Beta Rays

P. S. HENSHAW, Ph.D.,[2] R. S. SNIDER, Ph.D.,[3] and E. F. RILEY

As BETA RAYS ARE commonly emitted by the products of a chain-reacting uranium pile, it was decided to investigate their biological effects. Suitable beta-ray sources, technics of exposure, and methods of dose measuring were developed by Raper, Zirkle, and Barnes (1). Raper, Henshaw, and Snider have reported the effects of these phosphorus beta rays on the surface organs of rats and mice (2, 3). The biological effects described by them were primarily the more immediate (or acute) effects of irradiation.

Since the writing of the reports mentioned above,[4] clinical observations of the experimental rats have been carried forward by the present authors. In doing so, it was found that the terminal condition of the animals was, for the most part, a remarkable display of malignant activity and developmental abnormalities. This paper, then, will be devoted to a description and discussion of these final manifestations of beta-ray injury. Some preliminary comments on methods are necessary, however, since the detailed report on beta-ray exposure technics is not now generally available.

METHODS AND PROCEDURES

P^{32} was utilized as a source of beta rays in all the present experiments, this isotope being chosen from the list of beta-ray emitters after a consideration of such factors as availability, half life, and purity of radiation. To prepare P^{32}, the reaction $P^{31}(n,\gamma)P^{32}$ was used, with the pile serving as a neutron source (4). Since this isotope in a powdered form would have been virtually impossible to handle, equal parts by weight of amorphous red phosphorus and a phenolic-formaldehyde resin were combined and cast into sheets roughly 0.2 inch thick. Plaques of suitable dimensions were then cut from these sheets, activated, and used as sources.

Doses of beta radiation were expressed in rep. (roentgen equivalent physical), which is described as that quantity of beta radiation which produces ionization in tissue equivalent to 1 r. Several devices were used to measure the ionization produced by the emission from the activated plaques, the basic instrument being an extrapolation chamber similar to those described by Failla (5) and Quimby (6). The essential features of this instrument were (*a*) two parallel charged plates and (*b*) provisions for varying the distance between electrodes. With the use of this chamber and absorbers of different thickness, measurements of ionization were made (*a*) with the interplate distance varied and (*b*) with various thicknesses of absorber interposed between the source and the plate upon which the beta rays were first incident. From these measurements, an extrapolation was made to ionization per unit volume with zero air space and with zero wall thickness. This extrapolation then represented the ionization produced at the surface of a source plaque. All other instruments were calibrated against this chamber.

A second ionization chamber was developed which was similar to the extrapolation chamber, but more rugged, more easily operated, and with a fixed air volume. This chamber was also used to measure dose rate at various depths rela-

[1] This work was done at Clinton National Laboratory, Biology Division, Oak Ridge, Tenn., under Contract No. W-35-058-eng-71. Accepted for publication in February 1948.

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[4] These reports, while not now available for general distribution, will be published, according to present plans, by the Atomic Energy Commission.

tive to the ionization produced at the incident surface of an absorber. Again with the use of measurements of ionization with different thicknesses of absorber and extrapolation to zero absorber, the thickness which absorbed half the incident radiation was computed. It was then calculated that 0.8 mm. of soft tissue would absorb half the beta rays, correction being made for the relative densities of absorber and soft tissue.

For single, massive dose treatments of laboratory animals, a plastic box of appropriate size, completely lined with activated plaques, was used. (The plastic box served to hold the individual plaques and as shielding for laboratory personnel.) For these experiments, it was assumed that the intensity of radiation about an element of emitting surface varies (*a*) as the cosine of the angle formed by the perpendicular to the surface and the radius vector from the surface to the point and (*b*) inversely as the square of the distance from the emitting element. The rate at any point inside the source box, then, was assumed to consist of equal increments contributed by each element of solid angle subtending the point. A small pencil-shaped ionization chamber was constructed which, when inserted in the source box, measured this radiation from 4π of solid angle. Since objects as large as rats are opaque to beta rays, the dose rate at the surface of an animal inside the cubicle was corrected to half that from the 4π solid angle measured by the pencil chamber. Cages made of coarse-mesh, light-gauge screen were used to suspend animals centrally inside the source boxes and to keep the animals from ingesting part of the activated plaques. Since the wire screen absorbed some of the radiation, the experimental dosage rates had to be corrected for this factor by making measurements with the pencil chamber inside a sample cage. The dosage levels used were 1.5, 2.5, 3.0, 4.0, 4.5, 5.0, 6.5, 8.5 or 10×10^3 rep.

A different arrangement was used to administer small daily treatments. This was essentially a tunnel of source plaques through which animals, in mesh cages, were transported by means of a continuously moving belt. The length of the tunnel (number of plaques) and the rate of transport were adjusted frequently to give a constant dose despite the radioactive decay of the sources. For this series of treatments, a Victoreen r-meter chamber was adapted to measure radiation from 2π of solid angle. Prior to any series of treatments, this chamber was suspended in a cage and sent through the tunnel. The meter was so calibrated that total dose could then be calculated directly from the electrometer reading. The dose measurements were also roughly checked by taping dental size x-ray film to the body of a rat which was sent through the tunnel. The dosage levels used for this series of experiments were 0.5, 5.0, 50, or 625 rep. per day (six times weekly).

The animals were Sprague-Dawley rats obtained from an animal farm in Wisconsin, both males and females being used for this investigation. All rats were maintained in metal cages in an air-conditioned animal farm and fed Purina Fox Checkers. Control animals of two types were used: general controls kept in the animal farm without special handling and specific controls which were not irradiated but otherwise handled and confined as were the experimental animals.

RESULTS

Following single whole-body exposures to 4,000 rep. or above, acute changes in the skin began to appear at approximately one week, depending on the size of dose. First, there was a slight exudate in the eyes, followed within a day or so by a distinct skin erythema over the body. This in turn gave way to wet desquamation, loss of hair, and ulcer formation in various locations. Death, when it occurred, usually ensued within about four weeks. If it did not occur, the ulcers usually healed with slight surface distortions of the skin due to the contraction of scar tissue or to heavy crust formation.

Among survivors, various types of failure

and dysfunction were manifested in the epithelium and in the underlying connective tissues. In some areas wet desquamation continued for weeks, so that exudative material formed massive hard crusts on the surface. The skin that remained intact became thin and sometimes stretched tightly over the surface like an undersized garment. Hair growth was sparse and the hair itself became wiry in character. The external ears were destroyed as a result of radiation penetrating from both sides (4π solid angle exposure) and the eyes in many animals became opaque. In the derma, blood vessel abnormalities were manifested in the form of telangiectasia and the connective tissue became more fibrous. Neoplastic growths appeared in both the epithelial and connective tissue, the nature of which will be described below.

Among the animals receiving less than 4,000 rep., only a few of the changes noted above were seen, and then to a lesser degree. It was not possible to detect gross skin changes in any animals which received less than 1,500 rep.

In the case of the daily exposures, the acute symptoms in animals receiving 625 rep. per day resembled those following a single massive dose except that they came on more slowly and there was no recovery. Generalized atrophy continued and most of the animals were dead at ninety days. Those receiving 0.5, 5.0, and 50 rep. per day behaved essentially the same as controls except for a higher tumor frequency in the 50-rep. group.

Carcinogenic Effects

Figure 1 shows the appearance of certain experimental animals that received treatment. Animal A is representative of a group which received 4,500 rep. at four to five months of age, the photograph being made nineteen months later. The tumors were primarily epidermal, although occasionally subcutaneous types, over which the skin could be moved freely, were also present. Note that most of the external ear has disappeared, the eye is opaque and the hair sparse and wiry. A small amount of hair, which remained over the back, was clipped away in order not to interfere with the photograph. Animal B received daily treatments of 50 rep. per day six times per week for a period of eighteen months, making a total of approximately 23,000 rep., the picture being made nineteen months after treatment was begun. Both cutaneous and subcutaneous tumors arose in animals receiving this treatment, the latter occurring somewhat more frequently than in the animals receiving single treatments. The ears, eyes, and hair remained in better condition in animals treated daily than in those receiving single large doses of radiation.

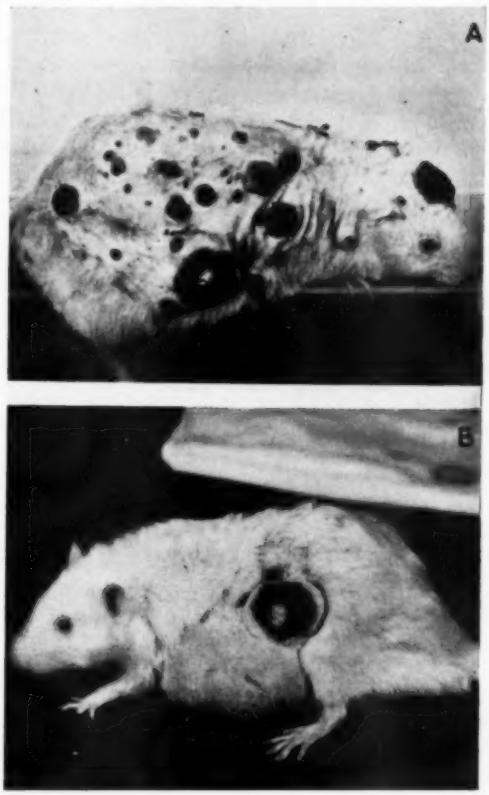

Fig. 1. Tumor-bearing rats. A. At nineteen months after receiving 4,500 rep. when four to five months old. B. At nineteen months after the starting of 50 rep. daily treatments.

Only males were used for the experiments with single massive treatments thus far carried out. Table I shows the results ob-

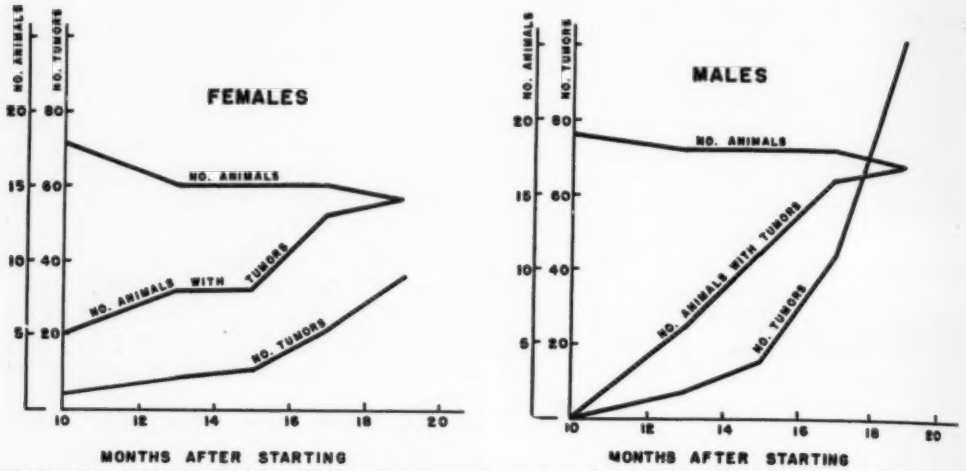

Fig. 2. Graphs showing survival, number of tumors, and number of animals with tumors, with respect to time after the beginning of daily treatments of 50 rep. per day.

tained for representative groups—general controls and those receiving 4,500, 6,500, and 8,500 rep.—giving the number of animals at the beginning of the experiment, the number that were surviving at eleven, fifteen, and nineteen months, the number of tumors that were present or had been present at any time, and a rough break-down as to tumor types.

The tumors seen were classified into two general categories, as mentioned—those involving the skin and those involving the underlying tissue. The former were expected to be largely epithelial in character

TABLE I: EXPOSURE AND TUMOR INCIDENCE FOR MALES AND FEMALES AT DIFFERENT TIMES

			11 Months After Starting					15 Months After Starting					19 Months After Starting				
Dose	Sex	Original No. of Animals	No. of Animals Remaining	No. of Animals Showing Tumors	Total No. of Tumors, All Types	No. of Subcutaneous Tumors	No. of Cutaneous Tumors	No. of Animals Remaining	No. of Animals Showing Tumors	Total No. of Tumors, All Types	No. of Subcutaneous Tumors	No. of Cutaneous Tumors	No. of Animals Remaining	No. of Animals Showing Tumors	Total No. of Tumors, All Types	No. of Subcutaneous Tumors	No. of Cutaneous Tumors
Single Treatments																	
G. C.	M	36	31	0	0	0	0	29	1	1	1	0	19	3	3	3	0
4,500	M	20	18	18	66	10	56	11	11	93	20	73	Dead				
6,500	M	40	33	31	125	26	99	13	12	142	43	99	Dead				
8,500	M	40	4	4	13	5	8	3	3	21	10	11	Dead				
Repeated Treatments																	
G. C.	M	20	17	0	0	0	0	17	3	4	4	0	15	4	5	5	0
G. C.	F	20	20	1	1	1	0	20	4	5	5	0	20	10	14	13	1
Sp. C.	M	20	20	0	0	0	0	19	0	0	0	0	17	1	1	0	1
Sp. C.	F	20	19	2	2	2	0	18	6	7	7	0	17	14	20	20	0
0.5 r	M	20	20	1	1	0	1	19	2	2	1	1	15	7	7	6	1
0.5 r	F	20	20	2	2	2	0	20	6	7	7	0	19	13	18	18	0
5.0 r	M	20	20	0	0	0	0	17	2	2	2	0	17	3	3	3	0
5.0 r	F	20	20	1	1	1	0	20	5	5	5	0	20	9	12	12	0
50.0 r	M	20	19	0	0	0	0	18	11	15	10	5	17	17	102	31	71
50.0 r	F	20	18	5	5	5	0	15	8	10	10	0	14	14	35	22	13

and the latter of connective-tissue type. Such a separation is interesting in that much more radiation was absorbed in the epithelium than in the underlying tissues.

Some of the effects were clear-cut. So far as males are concerned, in none of the 76 controls (including those for both single and repeated treatments) did cutaneous tumors develop, and in only four did a subcutaneous tumor arise within nineteen months after treatment.

At eleven months after exposure, 18 of the 20 animals which had been given a 4,500 rep. treatment were alive with tumors and 66 tumors had been seen, 10 being of the subcutaneous variety and 56 of the cutaneous. Thirty-three of the 40 rats receiving 6,500 rep. were alive and 125 tumors had been observed. The ratio of cutaneous to subcutaneous and the average number of tumors per animal was much the same. Only 4 of the 40 receiving 8,500 r were alive at eleven months, but all of these showed tumors. At fifteen months, more animals were dead and more tumors had been seen—otherwise, the picture was the same. All experimental animals were dead before 19 months.

Table I gives the same kind of information for both females and males, for general and specific controls, and for animals receiving daily treatments of 0.5, 5.0, and 50 rep. per day.

Taking the controls first, it is plain that, although the spontaneous incidence of cutaneous tumors was essentially the same among males and females, many more tumors of the subcutaneous type appear among females. *A priori* then, one begins to suspect that the subcutaneous tumors are associated with mammary gland conditions and that a somewhat different picture may be obtained for the two sexes.

Examination of Table I discloses that the results obtained with specific and general controls, and with animals receiving 0.5 and 5.0 rep. per treatment were essentially the same. In those receiving 50 rep. per day, however, the picture was different. Figure 2 shows the number of tumors appearing in animals receiving 50 rep. per day. The graphs indicate that the tumors begin to arise about ten months after the beginning of treatment and that all animals had tumors of some kind by nineteen months. Interestingly, while the spontaneous incidence of tumors was lower in males, the incidence in treated animals was much higher. Table I reveals that, of the 102 tumors in males, 31 were subcutaneous and 71 cutaneous, whereas of the 35 in females, 22 were subcutaneous and 13 cutaneous. Thus, the incidence of both types of tumors was higher in the 50 rep. per day group than in the other groups. This is true also for both sexes, but to a much more marked degree for males than for females.

Histopathology: Many questions arose which could be answered by microscopic examination. It was important to determine whether the skin lesions were uniform or different in type and in degree of differentiation. Likewise, it was desirable to know whether the subcutaneous tumors in males and females were comparable. Figure 3 shows an animal with a variety of proliferative lesions in different stages of development, ten months after a 4,500-rep. treatment. Biopsy specimens were taken from the locations marked and the letters permit one to associate the tissue specimen with the corresponding lesion.

Perhaps the most striking feature of these early lesions is the degree and variety of differentiation shown. There are thickening and downgrowth of the basal layer, pearl formation, hypertrophy of sebaceous glands, and vacuole formation. Most of these growths can be classified as basal-cell or squamous-cell carcinomas, depending on the morphological differentiation.

Figure 4 shows lower magnification of some of the lesions and accordingly the relationship to surrounding parts. It is apparent that the tumor starts as a thickening and downgrowth of the epithelial layers and that a high degree of specialization is present from the first. A shows a squamous carcinoma spreading beneath the epithelial layers; B, C, and D show small wart-like growths at the surface, with only slight evidence of downgrowth.

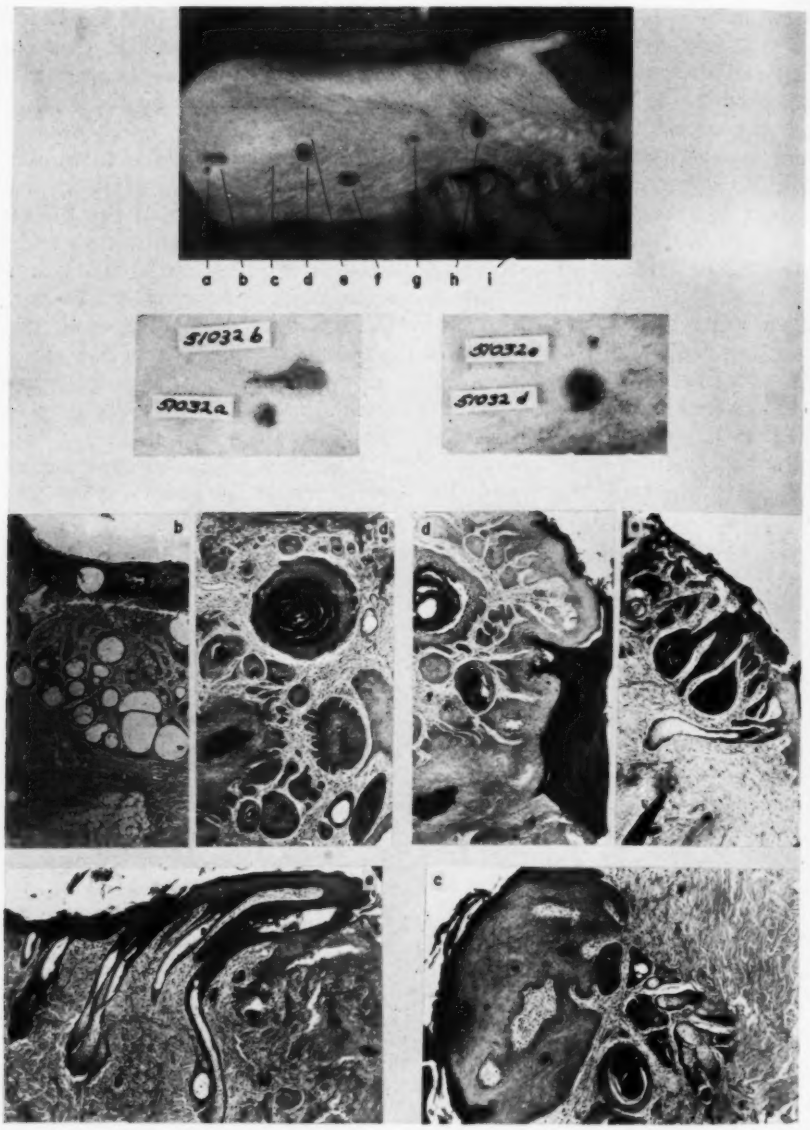

Fig. 3. Photographs of skin lesions and tissue sections (× *c.* 100). The letters on tissue sections indicate the particular tumor from which the section was taken.

Figure 5 shows conditions of the same type in another animal but with certain important additions. Section *e* is predominantly squamous carcinoma, but there is a suggestion of gland formation. Section *g* is clearly adenomatous, the structure strongly resembling mammary gland. Since the lesion from which this section was taken resembled a wart superficially, the question is raised as to whether mammary gland tissue was drawn up from beneath to form the growth as seen or whether the surface epithelium was induced to form this type of tissue. Because the lesion was so definitely a part of the surface epithelium, the latter possibility seems likely.

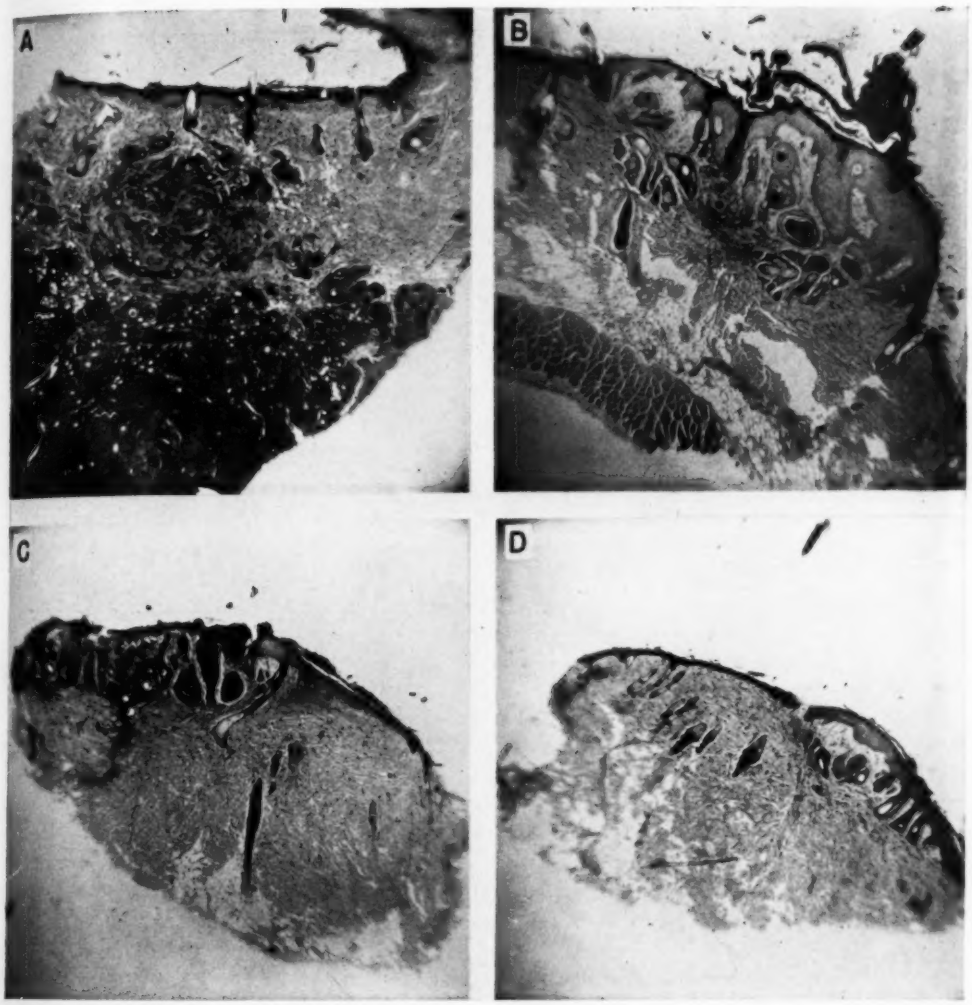

Fig. 4. Low-power magnification (× *c.* 45) of early lesions.

Section *c'* came from a massive subcutaneous tumor and is spindle-cell sarcoma with a tendency toward fibroma. Specimen *c* is a basal-cell carcinoma resembling mammary gland in some respect.

Figures 6 and 7 give some further indication of the varieties of tumors observed microscopically. Since it has not been possible to correlate particular tumor types with types or dosage of exposure, the histologic specimens were selected at random, disregarding the type of treatment. Figure 6, A, B and C, shows various expressions of basal and squamous-cell carcinomas. D and E of Figure 6 and A and B of Figure 7 are adenocarcinomas of rather bizarre types, showing uneven arrangement and variation in size of cells, difference in amounts of connective tissue, and slight evidence of secretion. D, Figure 7, shows such an excess of fibrous connective tissue as compared with glandular tissue that it may be called fibroadenoma of the mammary gland. E, on the other hand, shows excessive secretory products within the lumen of epithelial tubules. F shows

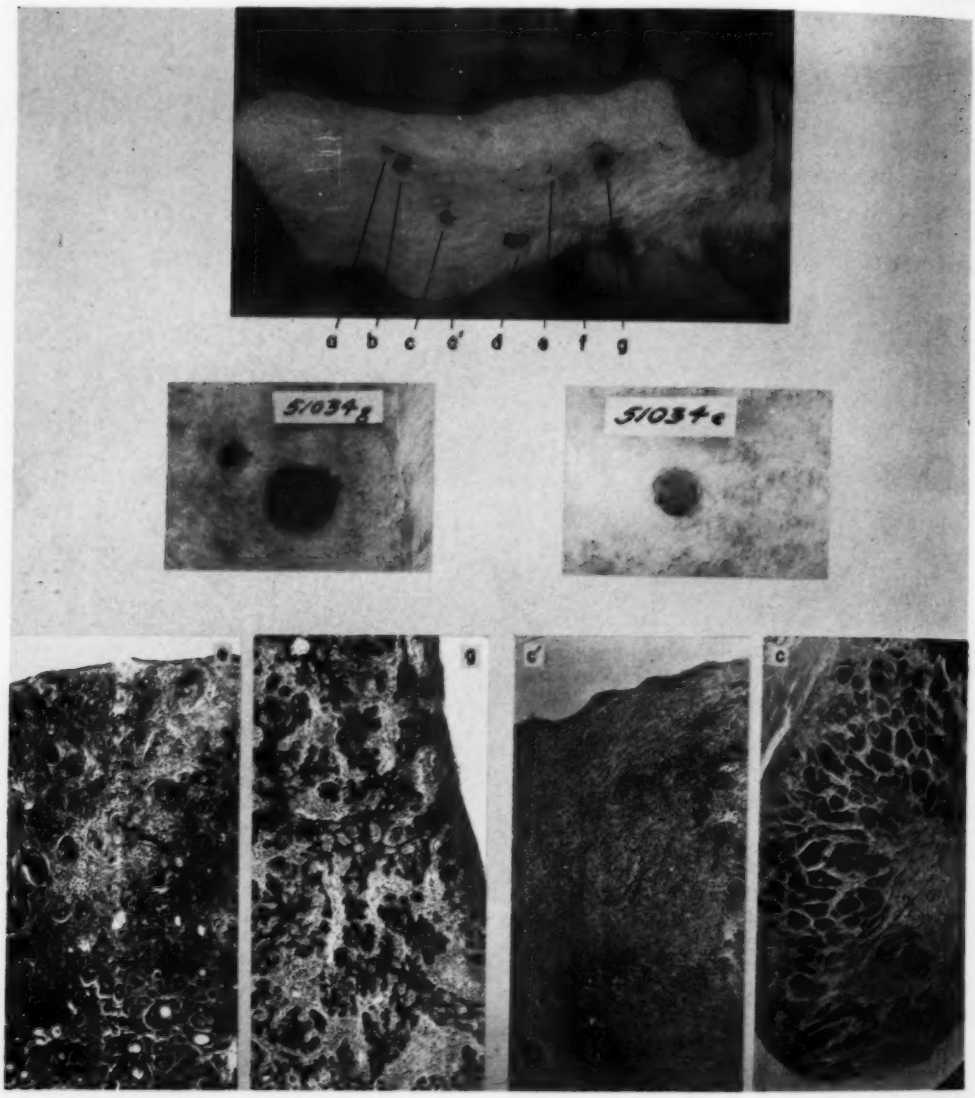

Fig. 5. Photographs of growth lesions and tissue sections (× *c.* 100) as in Figure 3.

fibrous connective tissue almost devoid of glandular epithelium, and G a spindle-cell sarcoma tending toward a fibrosarcoma. H presents a picture of extensive differentiation of connective tissue. In addition to the tendinous fibers formed, this tissue specimen displayed islands of cartilage and bone formation (not clearly seen in the photograph). Going back to Figure 6, photographs F and H show sebaceous gland hypertrophy bordering on adenoma. These figures illustrate only a few courses which the epidermal and connective tissues may take.

ABNORMALITIES OF OTHER TYPES

The exploratory character of this study followed an interesting course. The tumor manifestations were so striking that other important changes were overlooked for a

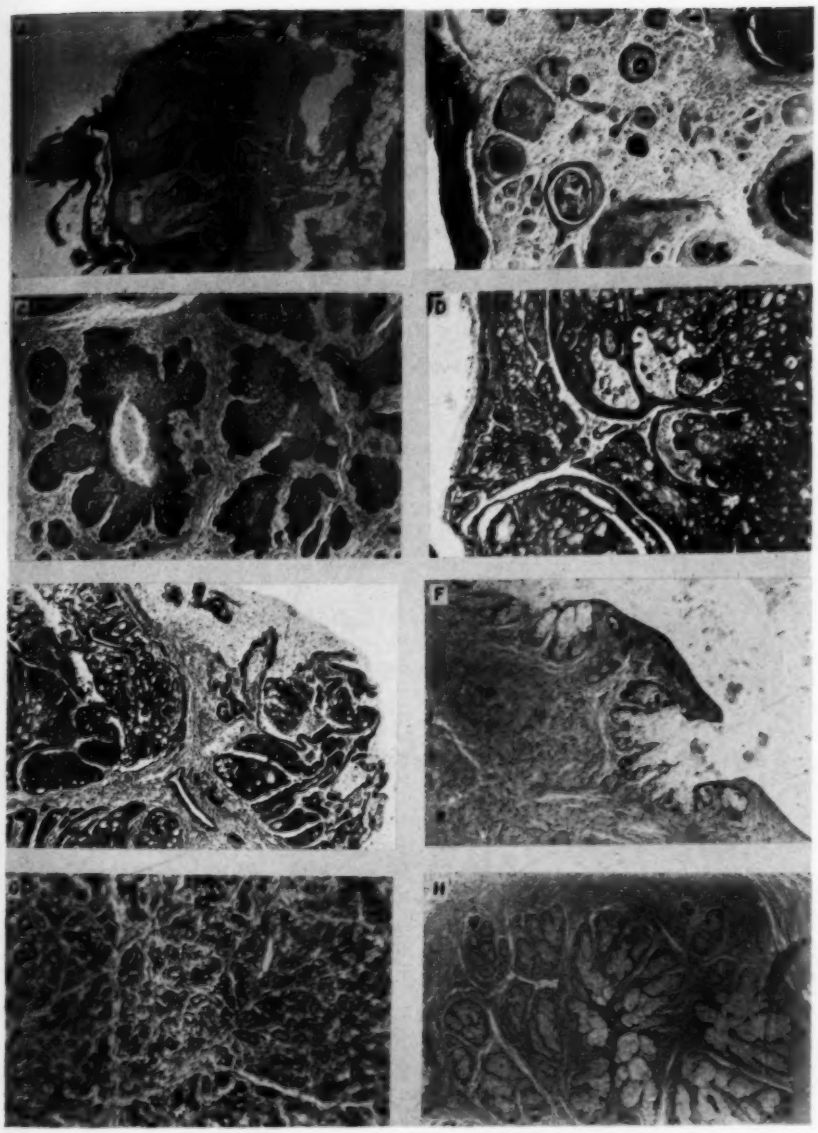

Fig. 6. Photomicrographs of growth lesions on animals that have received various treatments with beta rays, showing the wide diversity of types (×90, except G, which is ×190).

time. In fact, we were brought around to them by *a priori* reasoning. Having made sections of biopsy material taken early from skin lesions, and having seen the wide variety of malignant activity initiated by beta rays, we found ourselves asking why the induced behavior should always be of the malignant type. This led to a more thorough examination of the animals and a rewarding observation.

Figure 8 shows foot abnormalities which definitely were not of the malignant variety. A shows two toes with accessory claws. The toe at the left in the picture has a small claw-like appendage which runs more or less parallel to the main claw.

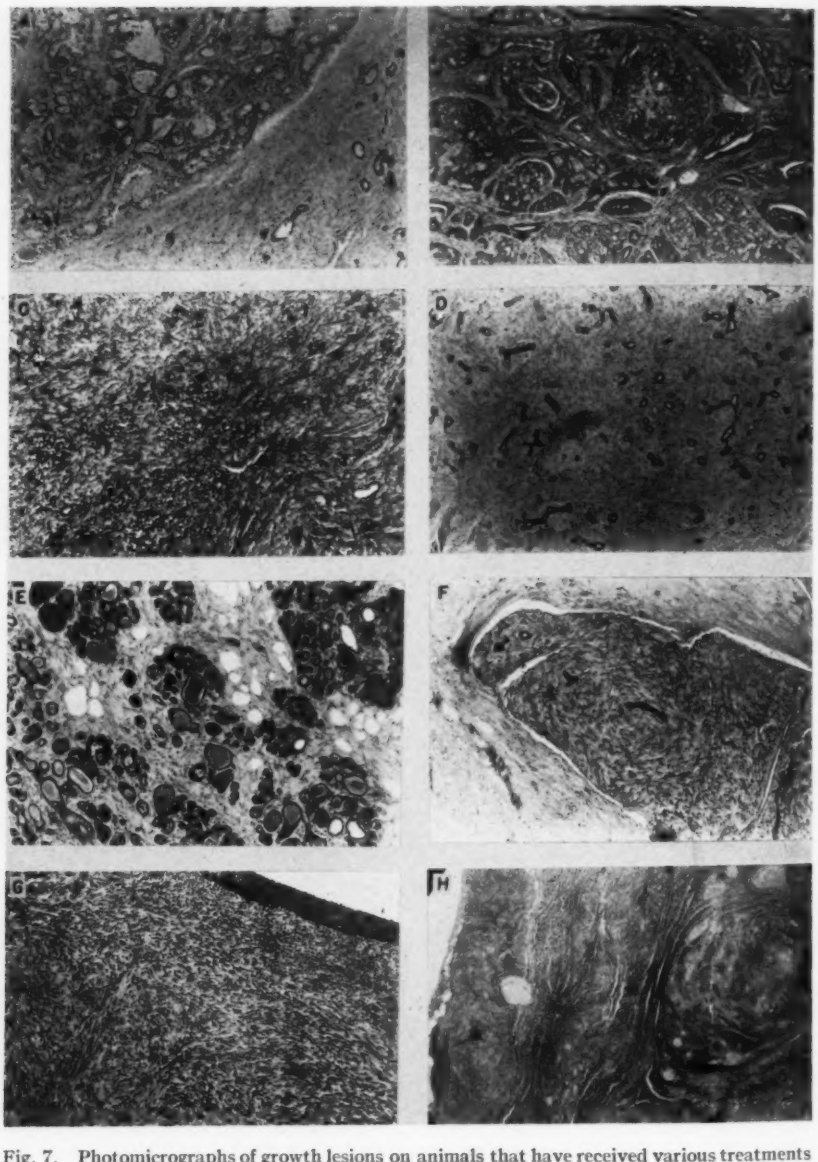

Fig. 7. Photomicrographs of growth lesions on animals that have received various treatments with beta rays, showing the wide diversity of types (×90).

The toe at the right shows an extra claw, almost as large as the main one, coming in from the side. Although the photograph does not show it, a third claw was present on this toe on the other side of the main claw. B reveals more plainly an extra claw coming in from the side, and C shows two toes each with extra claws arising from what ordinarily would have been toe pads. In some respects the extra claws in C seem to oppose the main claw in the same manner that the two parts of a lobster cheliped oppose each other. These abnormalities arose in animals that received

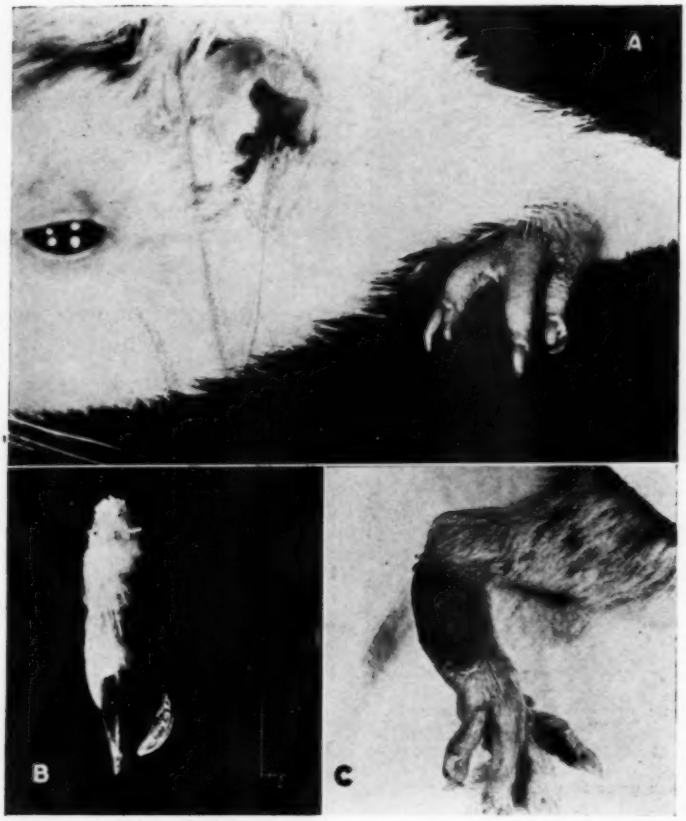

Fig. 8. Toe abnormalities in animals that received 4,000 to 5,000 rep. beta rays fifteen months previously. A. Note the large and small claw on one toe and three claws on the outside toe. B. Accessory claw growing at the side. C. Opposing accessory claws on two toes. Note the skin tumors on the foot.

4,000 to 5,000 rep. fifteen months previously, when they were two to three months old.

Figure 9 shows a soft-tissue extension from what obviously was a foot pad. Although this growth would probably have been found to be a benign papilloma, if examined histologically, it nevertheless represents an intermediate stage between the developmental abnormalities and the advanced malignant lesions.

Figure 10A displays a horn-like projection of chitinous-like material which excited attention at first, as it was thought that perhaps a remarkable new organ was being formed. Shortly after the time this photograph was made, however, the tissue beneath this structure rose up and formed a malignant tumor. B shows a two-pronged, pink, soft tissue extension which may be regarded as a papilloma, the same as the foot-pad extension. One would think little about such structures, as they sometimes occur spontaneously; but in the present case, where skin is giving rise to such a variety of unusual structures, it seems likely that radiation may have been instrumental in inducing them.

A Special Consideration: Figure 11 shows a response which deserves attention, although the result is not yet entirely clear. These animals received 8,500 rep. fifteen months previously. From Table I it is apparent that only 3 out of 40 animals receiving 8,500 rep. survived to fifteen months. Thus, although the dose was

Fig. 9. Soft-tissue extension of a foot pad on an animal that received 50 rep. of beta rays six times weekly. Note the tiny extra claw on the pad of the index toe.

large and the animals managed to survive, the tumor response was not nearly so great as in the animals receiving 4,000 to 5,000 rep. Not only were the tumors smaller which did form, but also there were fewer of them. This suggests an optimal dosage below 8,500 rep. for tumor induction. More observations will be needed to establish this very interesting possibility.

DISCUSSION

A point of particular interest coming from this preliminary investigation of the latent effects of P^{32} beta rays is the fact that tissue could be caused to elaborate one kind of abnormal growth and immediately adjacent to this to form another type of growth or remain quiescent. Further speculation about this diversity of response poses still another enigma. It is accepted that rapidly growing tissues of the body are especially vulnerable to radiation. In the present study, such tissues would be primarily those arising from the stratum germinativum and a small portion of the mesenchyme cells. At the time of irradiation, cells in all stages of differentiation from the stratum germinativum or mesenchyme cells were present. The question, then, is whether the causative agent compelled malignant growth to "take off" from the level of differentiation the cell happened to be in at the time of bombardment or whether the change was induced in a parent cell, and became manifest only after some differentiation had been completed.

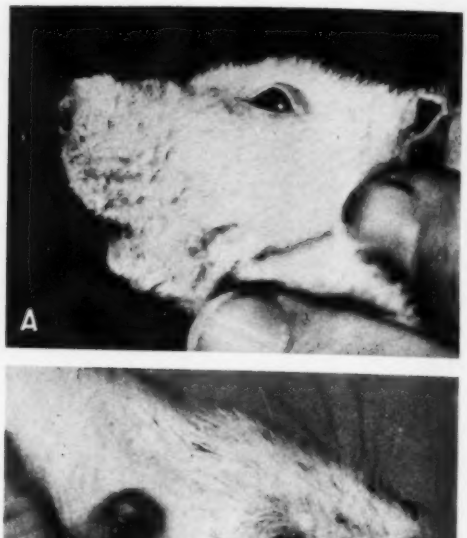

Fig. 10. Abnormalities on rats which received 5,000 rep. beta rays twelve months previously. A. Horn-like projection on the tip of the nose. B. Bifurcated soft-tissue extension on the side of the nose.

Because tumor formation and trauma often go hand-in-hand, one may be inclined to attribute etiologic significance to the trauma caused by beta rays. For in-

stance, in the case of large single doses, the stratum germinativum was destroyed to such an extent that wet desquamation occurred or ulcers were formed. Healing, if it did occur, was slow and then, after a period of reasonably satisfactory recovery, tumors and/or abnormal organs were formed. Trauma, in such a history, may have had a significant influence. Yet it is apparent from the series receiving 50 rep. per day that ulcerative break-down is not an essential precursor of malignant growth nor is it essential for the elaboration of unusual parts.

While the example of the series receiving 50 rep. per day tends to direct one's attention away from trauma as a causal factor, the possibility of a subliminal traumatic effect must not be disregarded. It is presumed that any amount of radiation, no matter how small, has the possibility of causing damage in the cells of the epithelium or connective tissue. Further, it may be presumed that the regenerative capacity of such tissues is adequate to compensate fully for such destruction only up to a certain point. Accordingly, subliminal damage as an etiologic factor remains a possibility so far as these results are concerned.

The results as presented show a greater tumor response in males than in females, but no good explanation for this result is available. Therefore, while this observation may be of some significance, it is not one which can be elaborated.

A final point of interest is the fact that the radiation, as applied, acted to guide cells into new and unusual pathways of development. Cells which have been destined to follow a particular pattern of growth were impelled, either by a single large dose or by small repeated doses, to follow a different pattern. These results offer the hope that the random action observed may be made selective and that cell destiny may be changed at will to be used to particular advantage.

SUMMARY AND CONCLUSIONS

1. P^{32} beta rays coming from phosphorus-impregnated plastic were applied to Sprague-Dawley rats in two ways: (1) single massive doses obtained with an enclosure-type treatment device and (2) repeated small daily doses (six times per week) obtained by passing the animals on a conveyer belt through a tunnel lined with the radioactive plastic.

2. Tumors of practically every type that can arise from skin and connective tissue appeared at ten months to one year after treatment.

3. Tumors arose in animals irrespective of whether they were receiving single or repeated treatments.

4. Epithelial tumors were almost absent in control animals, both males and females, but were present in large numbers in certain experimental groups. Subcutaneous tumors occurred in more than half

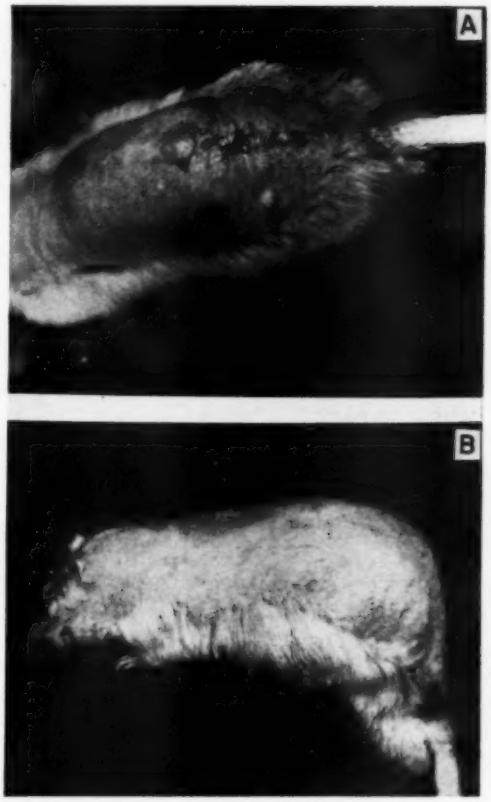

Fig. 11. Two animals pictured fifteen months after a single exposure to 8,500 rep. of beta rays. Compare with Fig. 1A.

the female controls but in control males only rarely. Treatment increased the incidence in females by only a few per cent, but in males many fold.

5. The optimal single dose treatment for tumor induction appeared to be in the range of 4,000 to 6,000 rep. In the case of repeated treatments, the 50-rep.-per-day treatments were most effective; however, since the dosage levels were widely separated, this cannot necessarily be regarded as optimal.

6. The tumors in many instances showed a high degree of differentiation, with a tendency for the epithelium to form squamous-cell and basal-cell carcinomas, as well as adenomas, and for connective tissue to form tendon, cartilage, and even bone.

7. Non-malignant abnormalities were also seen. These varied in type, consisting of accessory parts, such as extra claws on the toes, soft-tissue extensions, and chitinous projections from the feet and nose.

8. It is apparent that the radiation, as applied, was able to impel cells destined for a particular pattern of growth and development to change and enter into new channels of behavior.

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* MDDC Reports are issued by the Technical Information Division, Atomic Energy Commission, P. O. Box E, Oak Ridge, Tenn., for use within the Atomic Energy Commission.

SUMARIO

Desarrollo de Tejido Aberrante en Ratas Expuestas a los Rayos Beta Efectos Tardíos de los Rayos Beta del Fósforo[32]

Al exponer ratas blancas Sprague-Dawley a rayos beta procedentes de focos artificialmente radioactivos, midiéronse los coeficientes de exposición con varios instrumentos calibrados con una cámara de extrapolarización como patrón. Los tratamientos correspondieron a dos formas: (*a*) exposiciones masivas aisladas que variaron de 1.5 a 10 x 10^3 rep (equivalente físico en roentgens, o sea la cantidad de rayos beta que produce en los tejidos yonización equivalente a un r), y (*b*) exposiciones más pequeñas administradas seis veces semanales que variaron de 0.5 a 625 rep al día.

De acuerdo con la cantidad de exposición, comenzaron a aparecer varios trastornos del tejido cutáneo como a la semana del tratamiento, representando lo que cabría esperar en las lesiones irradiatorias agudas de la piel. En los animales que sobrevivieron la lesión aguda se presentó regeneración bastante satisfactoria, exceptuados los ojos, muchos de los cuales se volvieron opacos, y las orejas, que recibieron dosis excesivas y quedaron destruídas. Los tratamientos diarios no evocaron lesions agudas, salvo cuando alcanzaron el límite máximo de exposición, apareciendo entonces los síntomas agudos, sin ir seguidos de reposición.

Varios meses después de la reposición aparente de una lesión aguda o de la iniciación de los tratamientos diarios, presentáronse tumores cutáneos y subcutáneos por demás variados, observándose casi cuanta forma de tumor puede surgir de la piel y del tejido conjuntivo y encontrándose a menudo distintas formas lado a lado en

la misma zona cutánea. Después de ciertos tratamientos descubriéronse, en gran cantidad, epiteliomas, casi ausentes en los testigos. Hubo tumores subcutáneos en la mitad de los testigos hembras y rara vez en los machos; la irradiación acrecentó esa incidencia poco en las hembras, pero la multiplicó en los machos. Las exposiciones de 4,000 a 6,000 rep o de 50 rep al dìa parecieron ser las óptimas para la cancerogenia.

Además de los tumores, observáronse otras anomalías tisulares, siendo tan frecuentes las garras dobles o triples, las proyecciones quitinosas y las prolongaciones del tejido blando que la causa parecía residir en la irradiación más bien que en el azar.

Use of a Plastic Tracheal Cannula with Report of a Case[1]

JAMES C. BARNETT, M.D., IRA A. POLISAR, M.D. and ROBERT S. POLISAR, D.D.S.[2]
Brooklyn, N. Y.

THE PURPOSE OF this preliminary report is to present a new type of tracheal cannula which has proved useful both to the radiologist and to the otolaryngologist. The necessity for a plastic tracheotomy tube became apparent following several experiences with patients who had cervical neoplasms and who in turn wore tracheotomy tubes during their course of postoperative irradiation.

The actual construction of the new tube was undertaken by one of us (R.S.P.), using a non-toxic plastic methyl methacrylate, an acrylic resin which has proved to be safe through multiple cases of contact with the mucous membrane of the mouth. This plastic is one commonly employed in making dentures and, *per se*, initiates no reaction.

The principles used in metal tubes were embodied in this new tube and none of the advantages of the metal tubes has been discarded. There is merely a replacement of the outer metal tube with a plastic tube, and the patient continues at all times, except during radiotherapy and cleansing, to wear both the plastic outer tube and the metal inner tube. The original obturator of metal continues to be used when necessary, but the light weight of the new plastic tube permits delicate reposition many times without entailing the use of the obturator by the patient himself.

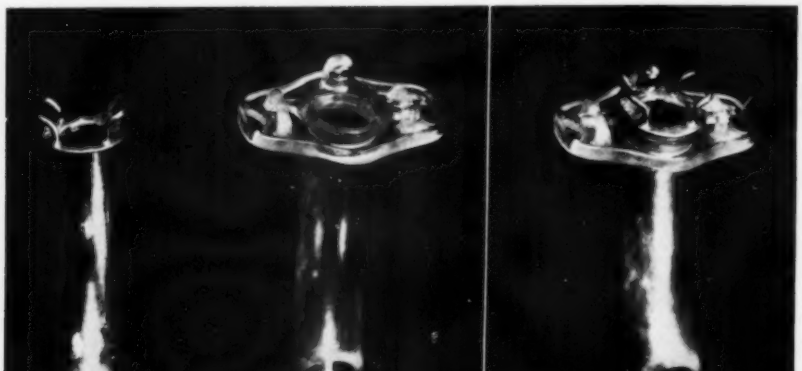

Fig. 1. Plastic cannula with metal inner tube removed (A) and with metal tube in place (B).

Formerly it was customary to remove the complete tube during deep x-ray therapy to prevent the inevitable and early-developing severe tracheal epithelite resulting from a combination of secondary and characteristic radiation from the metallic tube. Another consideration was the small partial "dead spot" behind the all-metal tube, to which radiation was considerably diminished. Daily removal of the tube was not only uncomfortable for the patient, but was also traumatic to the mucosa already injured by the therapeutic beam.

[1] Accepted for publication in February 1948.
[2] Department of Radiology, Department of Otolaryngology, and Department of Oral Surgery, respectively, Long Island College Hospital, Brooklyn, N. Y.

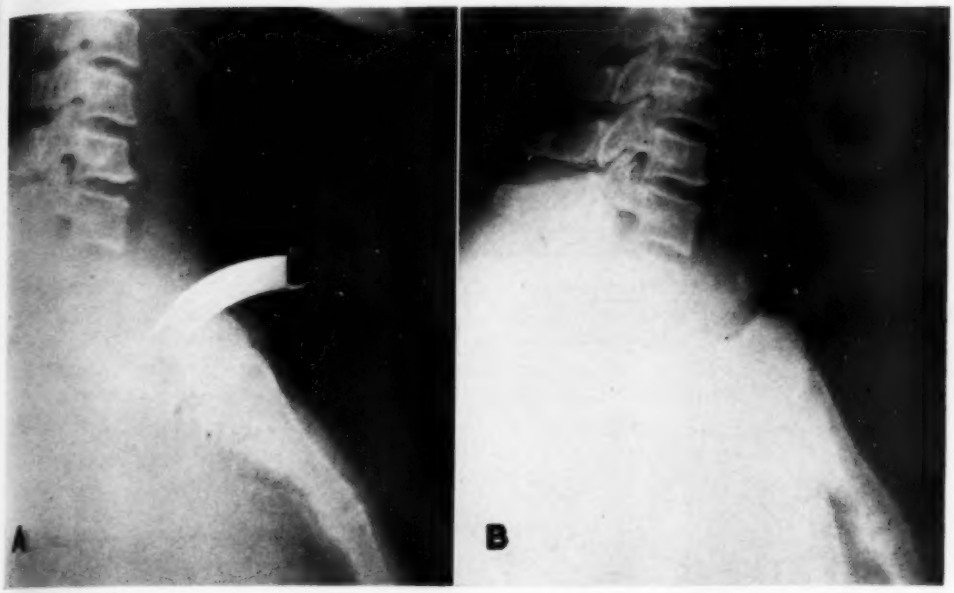

Fig. 2. A. Lateral roentgenogram showing complete cannula in place, including outer plastic shell and inner metal tube. B. Lateral roentgenogram showing cannula in place with metal tube removed.

Mr. C. B. Braestrup, Physicist for the Department of Radiology, Long Island College Hospital, measured the absorption of the new cannula in an x-ray beam. Using 175 kv. constant potential, he found that the tube absorbed 5.5 per cent of the total radiation. This is approximately the absorption percentage for equal thicknesses of soft tissue or water.

The new plastic tube was inserted in a patient who had undergone total laryngectomy about eight days earlier and remained *in situ* continually during the course of x-ray therapy, except for an occasional removal for cleaning. Irradiation was begun within four weeks of operation and a total of 6,800 r was given (3,400 r to each of two ports). Physical factors were 200 kv. and h.v.l. 1.9 mm. Cu; the output was 17.2 r/min. Two lateral oblique ports were used centered over the greater horn of the hyoid bone. For the first 2,400 r, two 10 × 15-cm. ports were used; for the remaining 4,400 r, the ports were reduced to 6 × 8 cm. The patient removed the inner tube and was able to prepare himself for the treatment without removing the outer plastic tube. The course of therapy was completed uneventfully and the patient will continue to wear the plastic tube until it is determined that no further intubation is necessary.

This is the first case at Long Island College Hospital to receive the full course of radiation therapy with continuous tracheal intubation. The patient experienced no unusual difficulty and maintained an excellent and clean airway throughout the entire treatment.

It is interesting to note that at one time the plastic cannula was removed for purposes of photography. Forty minutes later the tracheostomy stoma had contracted down to about 60 per cent of its former size. Reposition of the tube was slightly painful, recalling to us the times when patients using metal tubes were subjected to a daily reposition and redilatation of the stoma during the period of radiotherapy.

SUMMARY

A new type of plastic tracheal cannula has been described.

A case is reported in which continuous

tracheal intubation was maintained by this means throughout a full course of postlaryngectomy roentgen therapy.

NOTE: The authors wish to express their sincere appreciation for the advice and guidance extended by Dr. A. L. L. Bell, Director of the Department of Radiology, Long Island College Hospital, and Dr. Charles R. Weeth, Chief of the Department of Otolaryngology, Long Island College Hospital.

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SUMARIO

Empleo de una Cánula Traqueal Plástica, con una Observación

Con la nueva cánula traqueal descrita ha sido posible mantener la intubación continua durante toda una serie de roentgenoterapia postoperatoria. El nuevo instrumento comprende los principios de la cánula traqueotómica del pasado, pero el tubo externo, en vez de metal, es de una sustancia plástica, lo cual evita la necesidad de sacar todo el tubo durante la roentgenoterapia para precaver la inevitable y grave reacción consecutiva a la combinación de la radiación secundaria y característica derivada del metal. Comunícase un caso en que se empleó dicha canula.

A Rapid Cassette Changer for Angiocardiography[1]

MERRELL A. SISSON, M.D.
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THE FOLLOWING is a description of a simple, efficient cassette changer for use principally in angiocardiography. It permits the making of serial films at a speed faster than one per second. Usually, the first seven films are taken in four and a half to five seconds, and the rate is then slowed down so that the next four to six are finished in about fifteen seconds, depending on the problem under investigation.

The changer consists of three basic parts: a tunnel for 11 × 14-inch cassettes, a lever mechanism to release the exposed cassette and arrest the following unexposed one, and an "approach" board.

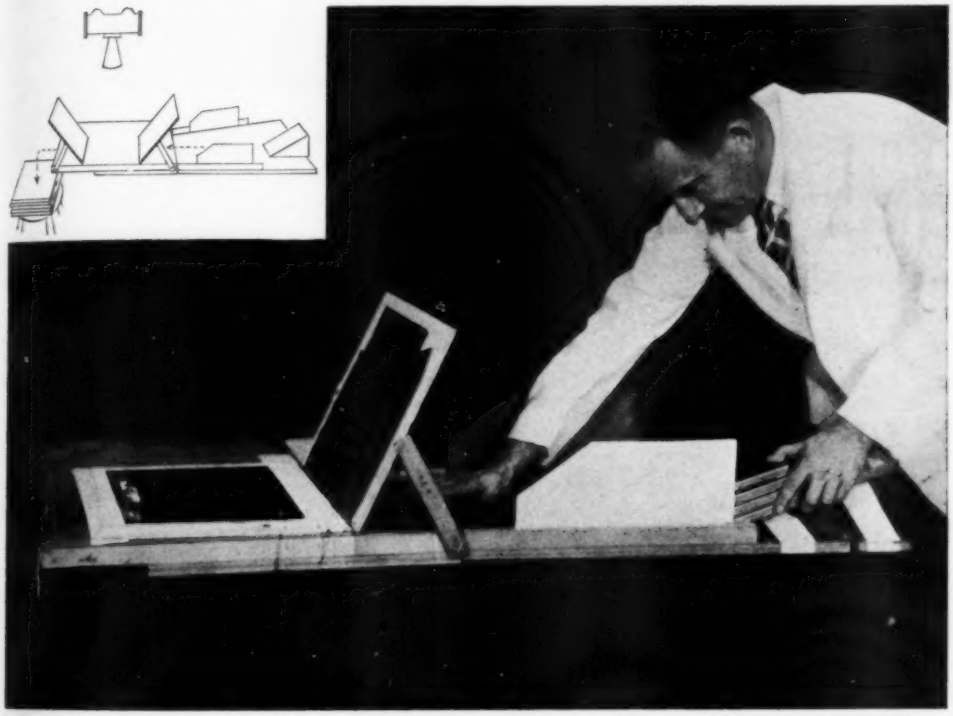


Fig. 1. The photograph shows one cassette just entering the tunnel, other cassettes on the 30° angle board, a lead shield for film and personal protection (a somewhat similar one, not shown, is attached on the left of the board), and the grid fastened with adhesive tape to the tunnel top. The diagram in the inset shows the "approach" board with angle board and side guides, tunnel with two lead shields in place, and a stand with exposed cassettes. An important construction detail is the short bottom board of the tunnel (see also 3A and dotted line of 3B).

The x-ray team requires a "pitcher," whose function is to push the cassettes through the tunnel and use the foot exposure switch (the anode rotating throughout the procedure), and a "catcher," who aids in removing the exposed cassettes.

[1] From the Department of Radiology, Stanford University Hospitals, San Francisco, Calif. Accepted for publication in February 1948.

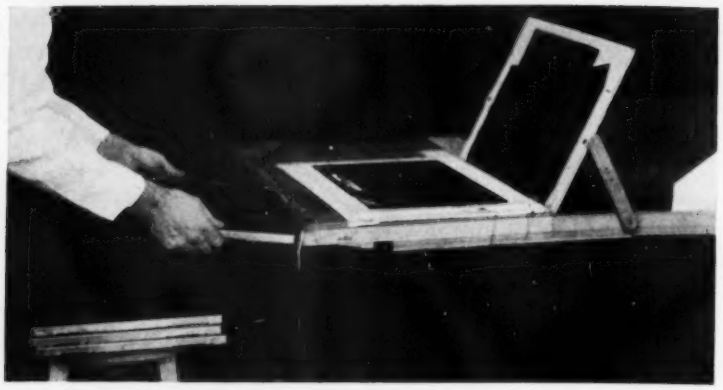


Fig. 2. The "catcher" receives and removes the exposed cassettes. Note that he aids the trailing edge of the cassette being removed, so that it drops down and away from the following cassette and thereby allows the "stop" time and room to spring back into place.

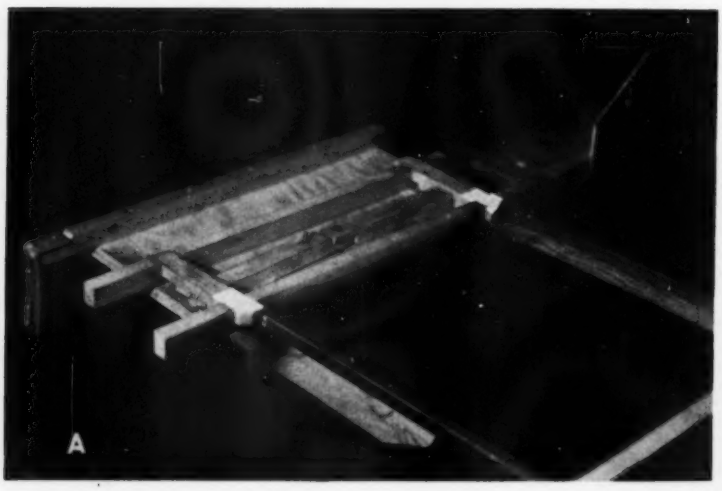
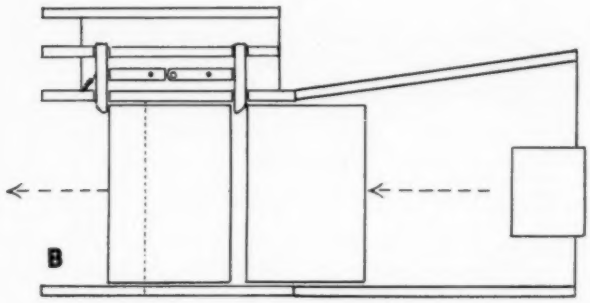


Fig. 3. A. The tunnel after the top is removed. The cassette in the foreground is in position of exposure, the one on the right is approaching the release accentuation bar of the lever mechanism. As this latter cassette moves further toward the left, *i.e.*, into the tunnel, this release block is thus pushed away and, through the lever mechanism, the sliding stop bar on the left moves away. Thus the incoming cassette can push the exposed one out of the tunnel. By a tension spring, the stop bar goes into place as soon as the exposed cassette drops below the level of the tunnel floor. In the photograph the tips of these two sliding hardwood blocks are painted white. The levers connecting these blocks have the fulcra placed so that a smaller movement of the release bar will cause greater motion of the stop bar. This allows for greater ease and dependability. (See also Fig. 3B.)

For the protection of these two radiologists and the films, lead-rubber aprons are worn and lead shields are in place on each side of the patient. Measurements of the scattered radiation, with the Lansford instrument, show that the radiologists are well protected for the usual number of exposures required. If however, three or four angiographic studies were done each day, the limit of tolerance, *i.e.*, 0.1 r would be approached. At the unprotected head of the table, where an anesthetist may be



B. Diagram of entire board, with top of tunnel removed, with cassettes in place as in 3A. The dotted line indicates the position of the tunnel bottom board. Note the tension spring fastened from the stop bar to the guide bar. This spring, which is incompletely shown in the photograph, should be fairly heavy.

working, the Lansford instrument measured 0.07 r during one entire angiographic procedure. With a reasonable volume of work, the surgeon and the anesthetist need no shields or protective aprons. However, in institutions doing much of this work (*e.g.*, four or more cases per day) mechanically operated apparatus would be preferable.

The illustrations show the general type and design of the equipment, and also examples of the films obtainable therewith. It may be noted that the original trial model is still in satisfactory use.

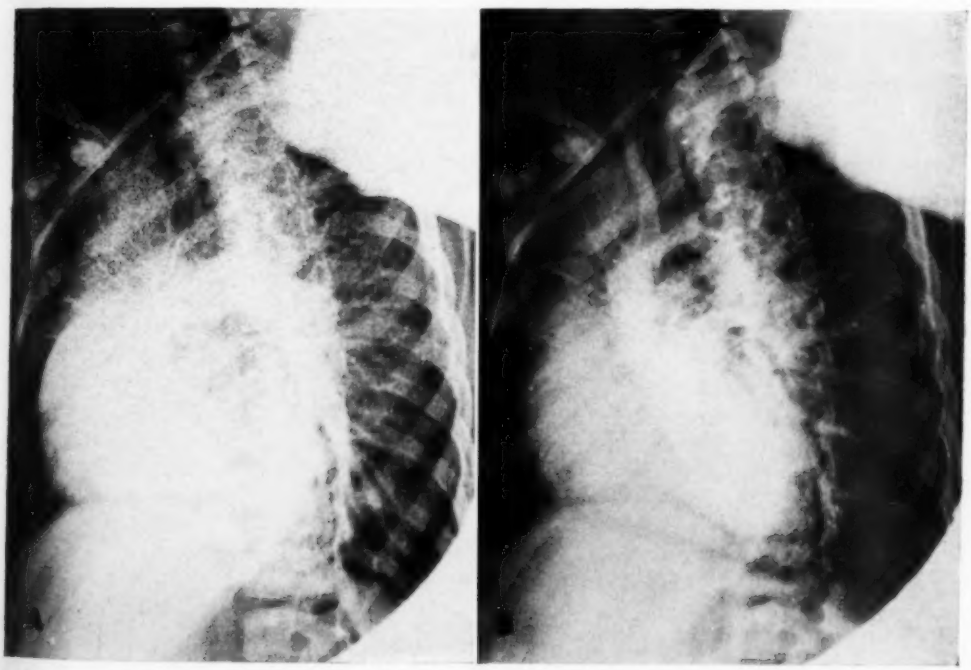


Fig. 4. A. The third serial film, in right posterior oblique position, showing residual diodrast in the right axillary vein, normal right auricle and ventricle, hypoplastic right pulmonary artery and normal or slightly enlarged left pulmonary artery, and some filling of the hepatic veins.
B. Normal left heart and vessels. This is the sixth film of the same angiogram.

ACKNOWLEDGMENTS: To Charles E. Grayson, M.D., for his design of the lever system, to A. Wayne Hackney, physicist, for the measurements of scattered radiation, and to Agnes Cameron for the drawings here reproduced, the author makes grateful acknowledgment.

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SUMARIO

Rápido Cambia-Chasis para la Angiocardiografía

El rápido cambia-chasis, aquí descrito para la angiografía, permite obtener radiografías seriadas con una velocidad superior a una por segundo. El dispositivo consta de tres partes básicas: un túnel para chasis de 27.5 por 35 cm, un mecanismo de palanca para soltar el chasis expuesto y contener el inexpuesto que sigue y un tablero de "aproximación." En los grabados adjuntos se verán los pormenores de la construcción y funcionamiento.

Photographic Effect of Various Radiations on Special Dental Packets[1]

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A CLEAR UNDERSTANDING of the photographic effects of various ionizing radiations is essential for the satisfactory formulation of a film-monitoring program.

The use of film for radiation measurements has been well studied by several investigators (3, 4, 5). Barkla and Martyn (1) in 1913 concluded that the photographic effect produced by x-rays of a given amount varies with the wave length. It has been demonstrated by Henny (2) that errors as great as 100 per cent may occur if the developing time is increased by one minute. Several writers have shown that quantitative errors seldom exceed 5 per cent when films of the same type and emulsion numbers are developed simultaneously, but a difference as great as 30 per cent should be expected if the films are developed at different times. This error may rise to 50 per cent or more if films of different emulsion numbers are used.

We would like to add some unmentioned causes of error. The storage of monitoring film is as important as the developing. Background fog or fogged film may be the result of any of the following:

1. Expiration date elapsed—old film.
2. Film that is not outdated, but stored in regions of high temperature.
3. Accidental exposure of film to radiation while in storage.
4. Storage of film in a room contaminated by any of the following fumes: ammonia, ether, formaldehyde, illuminating gas, or sewer gas.
5. Use of darkroom safe lights which are too bright or exposure of film to the safe light for too long a period.
6. Developing for too long a time or at too high a temperature.
7. Exposure to white light before fixation is complete.

There are only a few things which will impair development of the radiation effect on the film. One of these, and probably the most common, is the use of exhausted or partially exhausted developer solutions. Other factors are too short a developing time and a developer temperature below that recommended for the time used.

The present study was carried out with DuPont Dental Film #552-2, a special film which has been designed for monitoring programs. The film is packaged in a moisture-repellent light-tight wrapper identical with that used for the conventional DuPont dental film, #D-2, except that the customary lead backing is omitted. Each packet contains two pieces of film.

Throughout the study only fresh film which had been stored under favorable conditions was used. Fresh DuPont chemicals were prepared for each batch of film developed, and all developing was done at 68° F., for exactly six minutes.

The film as used in our monitoring program is generally worn in a numbered badge by persons working near ionizing radiation. It is usually worn for a period of one week before processing.

One of the pieces of film has a relatively thick layer of sensitized material and will show increasing degrees of darkening within a range of exposure of 0 to 3 roentgens. The second film has a thinner layer of sensitized material and will show progressive darkening after exposure to 1 to

[1] From the New England Deaconess Hospital, Boston, Mass., and the Laboratory of Pathology, Harvard Cancer Commission. This investigation was supported in part by Navy Contract N5 ORI-76, project No. 7. The radioactive phosphorus used was supplied by Clinton Laboratories and obtained on allocation from the U. S. Atomic Energy Commission. The paper was presented at the International Cancer Research Congress, St. Louis, Mo., Sept. 3–6, 1947, and was accepted for publication in January 1948.

20 roentgens. The indicated ranges of sensitivity are for radiation having a wave length similar to the gamma rays of radium. Radiation of longer wave lengths gives more darkening, as shown below. The films having the range of 0 to 3 roentgens are the only ones which proved useful to us in our monitoring program, since the exposure per individual, per week, was fortunately low. The following study is, therefore, concerned only with the more sensitive of the two films. Standardization was accomplished by exposing the film to carefully measured quantities of the various qualities of radiation.

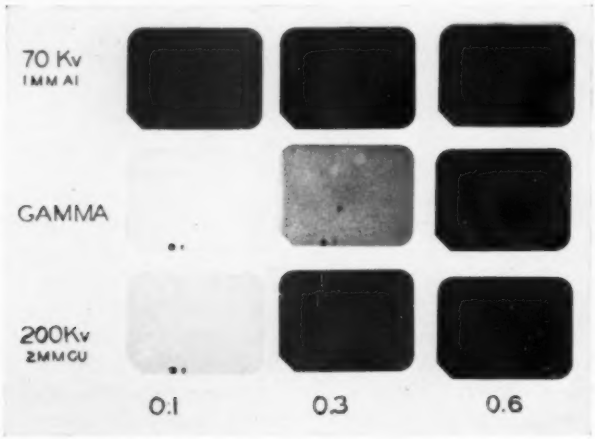

Fig. 1. Darkening of film exposed to radiation of various qualities in amounts of 0.1, 0.3, and 0.6 roentgens.

Gamma rays of radium were from a 25-mg. needle having a 0.5 mm. platinum wall. This needle has an active length of 25 mm. and was placed 2,400 mm. from the film. At that distance the size of the radiation field is approximately 3,000 mm. in diameter, giving a large ratio between the field size and active length of the radiation source, thus allowing the source to be treated as a point. The quantity received by the film was measured with a 0–0.1-r Victoreen Minometer chamber. The amounts were found to check within 5 per cent of the calculated dose when the value of 8.4 r per hour per milligram at 1 cm. was used, with the inverse-square law.

X-ray intensities were first measured with a Victoreen 25-r condenser type chamber. The film positions were established by the inverse-square law and were checked with the Minometer chamber.

All beta-particle intensities were measured with a milliroentgen meter manufactured by the Instrument Development Laboratories. The counter tube[2] with this meter has a glass wall of 30 mg. per square centimeter, or about 0.12 mm. thick. Using the formula derived by Feather (6), this thickness of glass will stop all beta rays having energies less than 0.38 Mev. The housing of this counter has a 2-mm. sliding sleeve of brass, enabling it to be used to measure gamma rays. It was used in this manner with gamma rays for calibrating its readings against the 0.1-r Victoreen chamber.

The radiation from the radioactive isotope, P^{32}, was from a thin layer of dehydrated salt, this layer being less than 0.2 mm. in thickness. As the counter tube will not register beta particles having energies less than 0.38 Mev., none of the films was exposed at a distance less than 40 cm. from the P^{32} sample. This distance was established by the Feather formula.

[2] Radiation Counter Laboratory Type 10-A Beta Ray Counter obtained from Tracerlab, Boston, Mass.

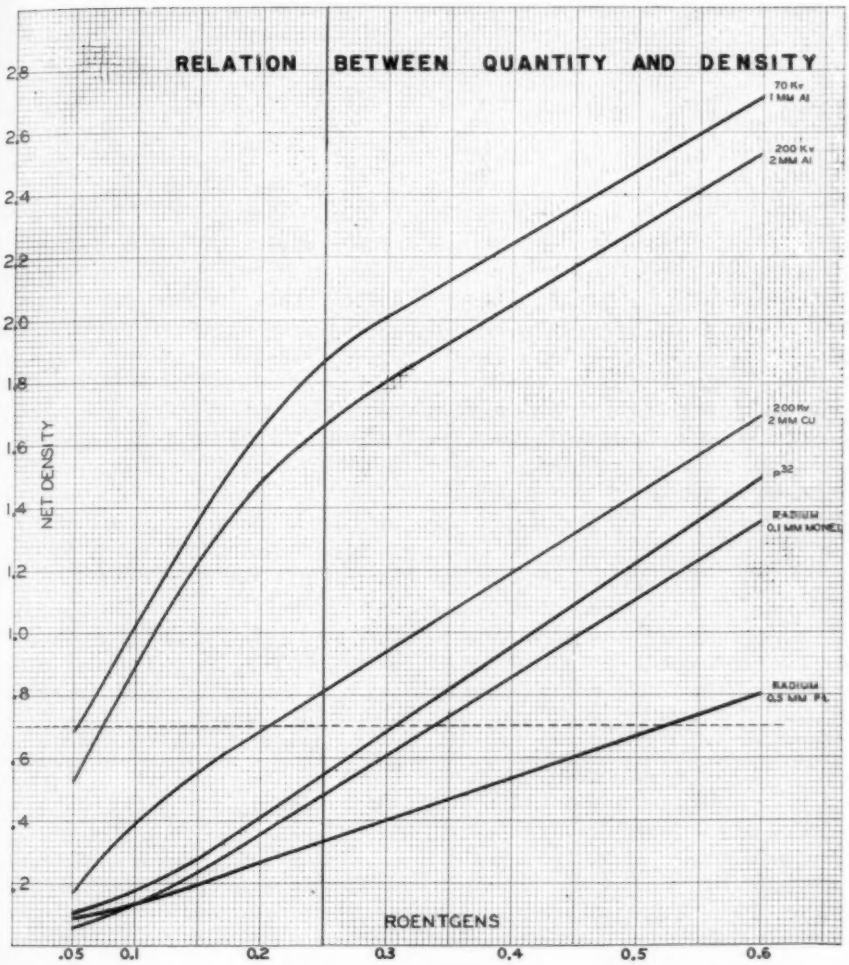

Fig. 2. Relation between quantity of radiation and density of exposed film for different qualities.

We have included the radiation effect from lightly filtered radium, as it is believed that its energy spectrum is fairly close to the spectrum of radioactive iodine, phosphorus, and sodium. The plaque used contained 20 mg. of radium and had a filter of 0.1 mm. monel metal. The intensity of the beta and gamma radiation was measured with the milliroentgen meter.

All comparisons of densities were obtained from several areas of each film, and the average of these areas was taken as the true density. For reading the densities, we have found a photo-cell type densitometer, such as the Ansco-Sweet, to be more satisfactory than the comparison method, since the errors due to eye fatigue and the human element are thus eliminated.

With each lot of film processed, two unexposed packets were developed and used for determining the background density. This density was deducted from the total density of the monitor or standardizing film to obtain the true density caused by radiation. After correcting for any changes in background, we have found that the densities for the various doses vary less than 10 per cent.

It is well known that the photographic effect is a function of quantity and also of

TABLE I: FACTORS OF RELATIVE EFFECTIVENESS TO PRODUCE A DENSITY OF 0.7

	70 kv., 1 mm. Al	200 kv., 2 mm. Al	200 kv., 2 mm. Cu	P^{32}	Radium, 0.1 mm. monel	Radium, 0.5 mm. Pt
Radium, 0.5 mm. Pt	10.6	7.0	2.6	1.7	1.6	0
Radium, 0.1 mm. monel	6.7	4.5	1.7	1.1	0	
P^{32}	6.2	4.1	1.6	0		
200 kv., 2 mm. Cu	4.0	2.7	0			
200 kv., 2 mm. Al	1.5	0				

the quality of the radiation. This effect was studied in 1913 by Barkla and Martyn (1). Failla (4) in 1931 presented a discussion regarding radium protection in which he pointed out the need of exposing the control film to the same quality of radiation as received by the monitor film. Fricke and Williams (7) have investigated the possibilities of using dental film for protection measurements; they also have found that the density of the film is dependent on the quality of radiation.

Figure 1 is a reproduction of films exposed to the following qualities of radiation: 70 kv. with 1 mm. Al filter, 200 kv. with 2 mm. Cu filter, and gamma rays from radium. The films were exposed to 0.1, 0.3, and 0.6 roentgens. It is evident from these films that the density does depend on the quality of the radiation. When exposed to x-radiation produced at 70 kv. with 1 mm. Al filter for 0.3 r, the film is very dark, whereas the same measured dose of gamma rays produces only a slight darkening. There is thus a definite variation of density of the film when exposed to equal amounts of radiation of different wave lengths.

Figure 2 shows graphically the relation between the quantity of radiation and density. We would have liked to carry the quantity to 1 r but were limited to 0.6 r by the fact that our densitometer is not capable of reading densities greater than 3. The broken line at density 0.7 in Figure 2 shows the variation of quantity for the various qualities of radiation.

To produce a density of 0.7, using 70 kv. with 1 mm. Al, a quantity of 0.05 r was required. To obtain the same density with gamma rays required 0.53 r or an increase of more than ten times. Table I shows the necessary increase of quantity for various qualities to produce a density of 0.7.

As shown in Figure 2, the photographic effect of this film when irradiated by 0.05 to 0.6 r is not linear for x-radiation, but it approaches a linear function on exposure to the beta particles of radioactive phosphorus or to rays from lightly filtered radium. With exposure to gamma rays, the effect is linear.

In the use of monitoring film, a complete set of characteristic curves for various radiations, to be used in interpretation of the film, should be compiled. With these curves and sufficient information regarding the quality of the radiation monitored, it should be possible to determine within 15 per cent the amount of radiation that has struck the film.

From our observations this film is reliable for protection measurements when the outlined precautions are taken. With proper processing, this film, when exposed to the same quality of radiation, can be calibrated to record the quantity within an error of 10 per cent.

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SUMARIO

Efecto Fotográfico de Varias Clases de Rayos sobre Ciertos Paquetes Dentales

Este estudio versó sobre el efecto fotográfico de diversas formas de irradiación sobre la llamada película monitora, es decir, una película dental especial que emplean las personas que trabajan cerca de rayos ionizantes para determinar la intensidad de la exposición. La película utilizada tenía una capa relativamente espesa de sustancia sensibilizada y en una escala de exposiciones de 0 a 3 roentgens reveló oscurecimiento cada vez mayor. La densidad se conformó, según se observó, tanto a la cantidad como a la calidad de la radiación.

Para producir una densidad de 0.7, usando rayos X con filtración por 1.0 mm. de aluminio, se necesitaron 0.05 r, pero para obtener la misma con rayos gamma, hubo que usar una dosis de 0.53 r, o sea el décuplo.

Con una irradiación de 0.05 a 0.6 r, el efecto fotográfico no resultó ser lineal para los rayos X, aunque sí se aproximó a éste cuando la exposición fué a las partículas beta de fósforo radioactivo o a los rayos de radio levemente filtrado. Con los rayos gamma el efecto fué lineal (Fig. 2).

De lo anterior dedúcese que al emplear película monitora, debe compilarse una serie completa de curvas características para las varias formas de irradiación. Con dichas curvas y con información adecuada acerca de la calidad de la irradiación, debe ser posible determinar con una aproximación de 15 por ciento la cantidad de radiación que recibe la película.

EDITORIAL

The Action of Radiation on Living Cells

It is obviously true that a better knowledge and understanding of the laws of growth of all types of cells will be necessary before many of the fundamental biologic problems in the fields of cancer research in general and radiation therapy in particular can be solved. The Committee on Growth of the National Research Council seeks to obtain information on these and related subjects. At one time, study of tissue cultures seemed to offer distinct possibilities along these lines, but the difficulty of growing cultures of epithelial and lymphatic neoplasms or cellular tissues with scanty stroma presents definite limitations. Limitations also exist in the amount of information which can be obtained from studying histologic sections because of their static nature, and it now appears that progress may be made from the development of radiochemistry of organic substances or the use of radioactive tracer technics including autoradiography.

Some of the early observations on the action of radiation on cells were made by British workers (1). They considered increased knowledge of the reactions exhibited by normal healthy cells necessary before the real nature of the processes initiated by radiation in tumors could be determined.

A successful two-day conference arranged by the British Institute of Radiology was held in London in the spring of 1946, when the general subject for discussion was "Certain Aspects of the Action of Radiation Upon Living Cells." Since the membership of the Institute includes those concerned with the production or application of ionizing radiation in medicine, biology, and physics, the officers emphasized both biologic and physical aspects in the papers and discussions. Among the topics included were "The Distribution of Ions Resulting from the Irradiation of Living Cells" and "The Action of Radiation on Viruses, Dilute Aqueous Solutions, Chromosomes, and Germ Cells, with Special Reference to Man."

From the standpoint of clinical radiotherapy, one of the most important papers was by Dr. P. C. Koller (3), who pointed out that the radiation effects on tumor cells induced by direct ionization were temporary and reversible, or permanent and irreversible. The most important temporary effect was suppression of mitosis. Data obtained from two squamous and two basal-cell carcinomas showed that the number of dividing cells was considerably reduced after 200 r, and that single doses of 400, 500, or 600 r suppressed mitosis for several days. Koller and Smithers (4) showed that, by taking into consideration recent cytologic investigations, a treatment method could be devised for individual tumors in which the total dose did not exceed 3,200 to 3,600 r. They demonstrated the importance of the mitosis-suppressing effect of irradiation on the treatment of tumors and the consequences of its dependence on the intensity or rate of flux. Experiments with pollen grains and a mouse sarcoma showed that an exposure given at a slow rate not only failed to suppress mitosis but also caused no delay in the development of the cell. Koller's observation of a patient with carcinoma of the tongue treated with radium at a rate of 0.5 r per minute indicated that the same was true for malignant cells in man. The practical application of this is evident. Data also showed

that the time of onset and the duration of mitotic suppression differed after the same dose in different tumors. This was attributed to the difference in the biologic activity of the tumors concerned.

Regarding the mechanism responsible for the suppression of mitosis, Koller observed that following irradiation the nucleoli in the nuclei of tumor cells were formed precociously. This early appearance of the nucleolus and the suppression of mitosis were phenomena which suggested that radiation altered the nucleic acid and protein-forming system of the cell which underlies cell division.

The permanent effects of radiation on the tumor cell consisted of gene-mutations and structural changes in the chromosomes. Dominant lethal gene-mutations could not be demonstrated directly; their occurrence could only be inferred from the death of cells without observable chromosome breaks. The radiation-induced structural chromosomal changes could be estimated quantitatively. The number of chromosome fragments seemed to vary with the dose. While in cells irradiated with 25 r, only one or two chromosome fragments could be seen, the number increased, after 100 r, to 2 or 3 and, after 300 r, to 4 or 5 per affected cell. Koller found instances in which the mean number of fragments per cell and the number of injured cells differed in cell samples taken from different regions of the same tumor after the same treatment. This difference in radiation response of parts of the same tumor could be due to differences in the radiosensitivity of the cell components. When irradiation was carried out by the fractionated method, chromosome segments which were already broken could be further damaged and fragmented by successive irradiation. This occurred when the mitotic-suppressing effect of irradiation covered the interval between two treatments.

The evidence indicated that most of the tumor cells were killed as a result of induced chromosome injuries. The injured cell may die during mitosis or after the completion of division, because chromosome injuries were evident throughout mitosis. The interval between fractionated doses must be long enough to allow the damaged tumor cell to recover and to enter mitosis. Observations by Koller on skin tumors showed that the dose required to induce chromosome disturbance was not more than 50 r to 100 r. A much higher dose was needed to kill tumor cells, irrespective of mitosis. Direct cell degeneration was observed after 3,000 r given as a single dose.

The different sensitivity of normal and malignant cells to radiation could be attributed primarily to the different life cycle of these cells. Koller found that chromosome fragmentation appeared in the bone marrow of the sternum twenty hours after 100 r, and that the number of cells affected and the mean number of fragments per cell were greater than observed in tumor cells after the same dose.

Tumors are affected both directly and indirectly by radiation. The indirect cell effect is accomplished by the radiation-induced changes in the normal cells and tissues which surround the tumor and form the supporting stroma. Tumors in the body could be successfully eliminated by 3,200 r, but 20,000 r or more may be required to destroy isolated tumor tissue *in vitro*. These phenomena suggested that normal tissue surrounding the tumor greatly increased the efficiency of radiation acting on the tumor itself.

After irradiation, the stroma reaction was greatly increased and accelerated. In skin tumors, and especially in carcinoma of the cervix treated by gamma rays, the number of plasma cells increased rapidly after 2,500 r to 3,000 r. Koller noted that the concentration of plasma cells was at its maximum five days after radium treatment. Degenerative changes could be seen twelve hours after a single dose of 3,000 r. No significant reaction was induced in the connective tissue below 3,000 r. When the interval between fractionated doses was unduly prolonged, the indirect effect of radiation on the tumor

was reduced to a negligible degree, the explanation being that injured cells recovered during the interval between two consecutive irradiations.

In conclusion, Koller pointed out that the different forms of radiation response represented only the various stages in cell and tissue reactivity and were interdependent. Because of great variability in onset, degree, and rate of different reactions, the tumor response as a whole is very complex. The immediate and most urgent task is to learn how to use the various radiation-induced effects more efficiently and with greater precision and economy. Progress in radiotherapy may be expected only if the introduction of more powerful sources of radiation is accompanied by a better understanding of the biologic basis of the various reactions of normal and abnormal cells and tissues.

A recent publication by Hall and Friedman (2) stressed the findings of acute cell death, progressive enlargement of cells to giant-sized tumor cells, and radiation keratogenesis. Their work is noteworthy in illustrating the practical value of serial biopsies in determining radiosensitivity and in acting as a guide to treatment.

The London Conference is evidence of continuing interest of British investigators in searching for the fundamental radiation effects. It is an effort worthy of support and encouragement, for many problems still remain in the field of radiation biology which can be solved only by more extensive basic research such as this.

It is heartening to know that steps in this direction are being taken by the Atomic Energy Commission in encouraging fundamental research by co-operation of universities in various parts of the United States, *e.g.*, the Brookhaven National Laboratory in New York and the Argonne Laboratory in Illinois. Surely this will lead eventually to advances in therapeutic radiology.

HAROLD W. JACOX, M.D.

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ANNOUNCEMENTS AND BOOK REVIEWS

SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY

The Sixth International Congress of Radiology will be held in London from July 23 to 30, 1950, with Congress headquarters at the Central Hall, Westminster. The address of the Central Office is 45 Lincoln's Inn Fields, London, W.C. 2. The officers of the Congress are:

President: Dr. Ralston Paterson
President Emeritus: Dr. A. E. Barclay
Vice-Presidents: Dr. S. Cochrane Shanks
Prof. B. W. Windeyer
Prof. W. V. Mayneord
Dr. F. Gordon Spear
Treasurer: Dr. H. Graham Hodgson
Secretary-General: Dr. J. W. McLaren

The program will be divided into four sections, each under the direction of a Vice-President, as follows:

Radiologic Diagnosis: Dr. S. Cochrane Shanks
Radiotherapy: Prof. B. W. Windeyer
Radiophysics: Prof. W. V. Mayneord
Radiobiology: Dr. F. Gordon Spear

The American Delegation is composed of representatives appointed by the four national radiological societies and by the Section on Radiology of the American Medical Association. The Members are:

American Roentgen-Ray Society: Delegate, Dr. B. R. Kirklin, Mayo Clinic, Rochester, Minn. Alternate, Dr. E. L. Jenkinson, St. Luke's Hospital, Chicago 5, Ill.

Radiological Society of North America: Dr. F. W. O'Brien, 465 Beacon Street, Boston 15, Mass. Alternate, Dr. John D. Camp, Mayo Clinic, Rochester, Minn.

American Radium Society: Delegate, Dr. Douglas Quick, 350 Park Avenue, New York, N. Y. Alternate, Dr. F. W. O'Brien, 465 Beacon Street, Boston 15, Mass.

Section on Radiology, American Medical Association: Delegate, Dr. U. V. Portmann, Cleveland Clinic, Cleveland 6, Ohio. Alternate, Dr. Edwin C. Ernst, 3720 Washington Boulevard, St. Louis, Mo.

American College of Radiology: Delegate, Dr. Ross Golden, Presbyterian Hospital, New York 32, N. Y. Alternate, Dr. B. P. Widmann, 250 South 18th Street, Philadelphia 3, Penna.

At a meeting of the Delegation held at the Palmer House, Chicago, on Sept. 14, 1948, under the Chairmanship of Dr. Arthur C. Christie, President of the Fifth International Congress, Dr. Ross Golden was made Chairman of the American Delegation.

Travel Arrangements: The officers of the Sixth International Congress in London have selected Thomas Cook & Son as the official travel agency of the Congress. The American Delegation has made the same selection, believing that the best co-ordination of arrangements on both sides of the Atlantic can be secured in this way. Thomas Cook & Son will make a reservation of space so that American members of the Congress who desire to do so may travel across the Atlantic as a group. Inquiries and reservations should be addressed to Mr. C. L. Hill, Thomas Cook & Son, 587 Fifth Avenue, New York 17, N. Y. *However, any individual is at liberty to make arrangements with a travel agency of his own choosing.* The officials of the Congress in London, as well as representatives of several travel agencies, have expressed the opinion that transatlantic travel will be unusually heavy in the summer of 1950, and have emphasized the importance of making *round trip reservations* as early as possible.

The Program: Details concerning the organization of the program have not yet been received from the London office of the Congress. They will be published later. Applications for a place on the program should be addressed to Dr. Ross Golden, Presbyterian Hospital, 622 West 168th Street, New York 32, N. Y.

LOS ANGELES RADIOLOGICAL SOCIETY

The recently elected officers of the Los Angeles Radiological Society, to serve for the ensuing year, are: Dr. John McAtee, President; Dr. Leo Levi, Vice-President; Dr. Wybren Hiemstra, 1414 S. Hope St., Los Angeles 15, Secretary; Dr. Wilbur Bailey, Treasurer.

LOUISVILLE RADIOLOGICAL SOCIETY

At the December meeting of the Louisville (Kentucky) Radiological Society, Dr. Clyde McNeill was elected President and Dr. Everett L. Pirkey, 323 East Chestnut St., Louisville 2, Secretary-Treasurer.

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA

The latest addition to the roster of state radiological societies is the Radiological Society of South Dakota. The Society will meet during the annual session of the South Dakota State Medical Society. The officers are: Dr. P. V. McCarthy, President; Dr. D. H. Breit, Vice-President; Dr. Marianne Wallis, 1200 East Fifth Ave., Mitchell, Secretary-Treasurer.

ROCHESTER ROENTGEN-RAY SOCIETY

The Rochester Roentgen Ray Society has elected the following officers for the year 1949: President,

Dr. George H. Ramsey; Vice-President, Dr. E. Forrest Merrill; Secretary-Treasurer, Dr. Ralph E. Alexander, 101 Medical Arts Building, Rochester 7.

SAMUEL FREEDMAN LECTURES ON DIAGNOSTIC ROENTGENOLOGY

On Saturday and Sunday, April 30 and May 1, 1949, Dr. LeRoy Sante, Professor of Roentgenology at St. Louis University, will deliver the first annual Samuel Freedman Lectures on Diagnostic Roentgenology at the University of Cincinnati College of Medicine. Roentgenologists desiring to attend are requested to write Dr. Benjamin Felson, X-Ray Department, Cincinnati General Hospital, Cincinnati, Ohio, for further details.

HONORS FOR DR. DEL REGATO

It is a pleasure to announce that at its meeting in December 1948 the National Academy of Medicine of France awarded to Dr. Juan del Regato, formerly of the Ellis Fischel State Cancer Hospital, Columbia, Mo., now Director of the Penrose Cancer Hospital, Colorado Springs, the *Chevillon* prize for his work on transvaginal roentgen therapy. This prize is awarded annually for "outstanding work in the treatment of cancer."

NEW FILM-CASSETTE CHANGER

Radiologists, especially those on duty with the Armed Forces, will be interested in the new lightweight film-cassette changer for taking stereoscopic views of the human chest which has been developed for military field use by the Engineering Development Division of the Army-Navy Medical Procurement Office at its Fort Totten, N. Y., laboratories.

The new apparatus weighs only 75 pounds and has a volume of only 4.6 cubic feet. Being light and compact, it can be fitted in a specially constructed case for air transport or can be conveniently hand-carried by two men. The lightweight construction has been attained by a unique design which eliminates the use of the usual heavy counterweights. Though it was necessary to employ 10 pounds of lead in construction of the conventional protective screen, further weight reduction has been achieved by the use of lighter metals elsewhere, principally aluminum.

The unit has a demountable base which is easily removed and, in order to simplify its manufacture for the Armed Forces, standard shapes of metal tubes, angles, channels, and sheets were used in its construction.

The cassette-changer mechanism is gravity-operated and is provided with both a magnetic and manual release, which shifts the cassettes in one and one-half seconds. The apparatus is so rigidly constructed that it is entirely free from vibration at the end of the shift period and the second exposure can be made immediately.

Letters to the Editor

BIOPSY IN THE DIAGNOSIS OF BONE TUMORS

Following the publication in the November issue of RADIOLOGY of the editorial by Dr. James F. Brailsford on "The Serious Limitations and Erroneous Indications of Biopsy in the Diagnosis of Tumours of Bone," several communications have been received by the editor, protesting the advocacy of a policy of delay in the diagnosis and therapy of bone tumors. Because of the wide divergence between the views expressed in the editorial and those of our correspondents, it has been decided to publish two representative communications, with the hope that frank discussion may help to clarify the subject. These letters were forwarded to Dr. Brailsford, and his reply is also printed. Some of the statements both pro and con would appear rather extreme to most experienced radiologists.

To the Editor of Radiology

DEAR DR. DOUB:

Had the recent editorial by Brailsford on the subject of neoplasms of bone appeared in your silver anniversary issue, one could have assumed that it was a reprinted essay from your first year of publication. At that, the responsible status of the histopathologist in 1925 was such that even then many clinicians, and perhaps some radiologists, believed that his opinion of osseous lesions was helpful. The notions expressed in this editorial are more consistent with those held by the more cynical of Virchow's contemporaries in a period which antedates your editorialist by a full century but to which he elects to return with an intellectual abandon alarming to most students of osseous pathology.

During the last decade an occasional radiologist, impressed by his diagnostic successes, has asserted that radiographic accuracy of diagnosis in tumors of bone is equal to that afforded by histological studies. Brailsford is the first to imply that scientific interpretation of altered osseous shadows has achieved such a degree of diagnostic acumen that the microscopist can be excluded from the field with benefit to the patient.

These radiological intellectual excesses are in part due to not infrequent errors in the interpretation of bone lesions by the microscopist, for the histopathology of bone tumors is difficult and complex, and the histogenesis of certain neoplasms of bone is not yet established. Examples of the diagnostic perils of microscopy are the healing callus line resembling a sarcoma, and the alarming appearance of the epiphyseal chondromatous giant-cell tumor (or chondroblastoma) of children which before Codman's recognition of its benign nature was, and occasionally still is, designated as "osteogenic" sarcoma. But only sophomore medical students believe the microscope to be an exact tool of diagnosis; others realize

that it is no better than the cerebral cortical activation provoked by its use. Histologic miscues by pathologists of experience can be more than matched with radiographic errors by competent radiologists.

A method of diagnosis depending on such gross morbid changes that four-fifths of a vertebral body has to be destroyed by osteolytic metastasis before shadow-discernment may be possible is hardly to be regarded as a fine measure of differential diagnosis. Experiences of the writer establishing the microscope several notches above the x-ray tube include some rude shocks to the radiologic ego. A woman, for example, presented a "characteristic" roentgenogram of peripheral, sclerosing osteosarcoma of the femur, as "classical" a picture as any textbook affords, which proved, after amputation without biopsy, to be metastatic from an occult mammary carcinoma. A similar case in a male, similarly managed, proved to be a metastasis from a prostatic carcinoma, while still another metastatic process was thought to be non-suppurative osteomyelitis.

Bone sarcoma can be cured by surgical ablation in a small percentage of instances, but deforming surgery should not be done until a diagnosis is made. Diagnosis should depend on the accumulated data of clinical, radiographic, and histologic evidence, which is wearisome repetition of established fact. Formal biopsy of bone sarcoma to obtain routine paraffin (not rapid frozen) sections is a safe procedure, for Crowell has repeatedly shown from the Registry of Bone Sarcoma that more of the cured than the fatal cases had biopsy done one day to five years before amputation. Budd and the writer have published data indicating that bone sarcomas have an inherent predetermined biologic growth potential, the degree of which determines curability or incurability with little respect to early treatment, biopsy, or even rude surgical insults.

There is accumulating clinical evidence that certain of the low growth-potential bone sarcomas can be cured by local resection, especially some of the fibrosarcomas and chondrosarcomas. This sort of therapeutic evolution is made possible by an increasing knowledge of histopathology, and on histologic evidence only can cases suitable for such conservative surgical measures be selected.

The pathologist and the radiologist are mutually dependent in the diagnosis of bone tumors. Microscopic interpretation of bone lesions requires correlation with radiographic evidence of the behavior pattern of the process. Evidence of neoplastic activity and stromal response can be rather accurately determined by the experienced radiologist, but even with serial radiographs of an advancing lesion he lacks the fine histological criteria of accurate differential diagnosis.

Yours sincerely,

IAN MACDONALD, M.D.

Department of Surgery, School of Medicine,
University of Southern California

To the Editor of Radiology

DEAR DR. DOUB:

As a rule, I read and enjoy RADIOLOGY without comment, but after studying the editorial by Dr. Brailsford in the November issue I feel impelled to protest. Dr. Brailsford's idealized aspect of the reliability of roentgenological diagnosis of bone tumors and his adherence to the "wait and observe" school in formulating the diagnosis are widely known. Fortunately, I believe, his beliefs are not so widely held. Roentgenologists who are frequently faced with the problem of diagnosing bone tumors and who, at the same time, are in a position to have their opinions proved, know that they are far from infallible. While erroneous pathological opinions do occur, they are extremely infrequent for the trained pathologist. The pathologist has demonstrated again and again that his is the most reliable source of diagnosis for bone tumors. Experience indicates, particularly in the obscure case, that the correlation of the clinical, laboratory, roentgenological, and pathological features is the best way to formulate a diagnosis of bone tumor. But experience also teaches that of these, pathological examination is far and away the most reliable.

I believe that most physicians in this country hold prompt amputation to be the treatment for osteogenic sarcoma, and they know that delay and procrastination in the guise of "observation" almost certainly have saved no limbs but have probably contributed to the high mortality in this disease.

There is one main point I wish to make. Publication of this controversial material in editorial form without explanation on the part of RADIOLOGY seems most unusual, and, it seems to me, a deviation from the past editorial policy, where discussion of both sides of a question was always included. By their silence, the editor and staff would seem to support Dr. Brailsford's ideas—ideas which I think are contrary to generally accepted teachings and which are unsupported by facts and figures. I therefore suggest, if this seems reasonable to you, that you present the viewpoints of those opposed to the concepts of Dr. Brailsford in the field of diagnosis and treatment of tumors of bone.

Yours sincerely,

ROBERT S. SHERMAN, M.D.

Attending Roentgenologist
Memorial Hospital, New York

To the Editor of Radiology:

DEAR DR. DOUB:

Thank you for allowing me to see the criticisms of Drs. Sherman and Macdonald of my editorial on "The Serious Limitations and Erroneous Indications of Biopsy in the Diagnosis of Bone Tumours."

As a guest in your country I will resist the temptation to respond to the sarcasm, for my critics are very vulnerable. It is unfortunate that neither of

them shows that he has taken the trouble to read the article of which my editorial is but a synopsis—"one may lead a horse to water; twenty cannot make him drink."

It would seem reasonable advice to Dr. Sherman that he should either (1) drop the study of radiology, since he expresses so little confidence in it, or (2) take up the subject of histopathology, for which he is so enthusiastic an advocate, or, as a poor substitute I feel, endeavour to gather "confidence" in radiology from the mass radiographic survey enthusiasts who claim for it superiority over clinical methods. He does not apparently realise that prompt amputation has resulted and will continue to result in the indefensible sacrifice of limbs (and life) for benign lesions (in spite of or because of biopsy) which would have resolved if they had not been subjected to useless surgery.

Delay and procrastination, if they can be so called, provided they are associated with careful and radiographic periodic observation will prevent this: occasionally it may ultimately be found that the lesion is, after all, malignant. This is justifiable since, even with long studious cultivation of my "idealised aspect of the reliability of roentgenological diagnosis of bone tumours," it has been my sad experience that prompt diagnosis and immediate amputation without any preceding biopsy have not resulted in cure of osteogenic sarcoma. Metastases can be demonstrated in some cases which attend hospital within a few weeks of onset and early recognition of the lesion. I do not believe the more the biopsies a lesion suffers, the less malignant it becomes. Macdonald's criticism may well be countered by a quotation from James Ewing: "Few surgeons realise the limitations in the histological diagnosis of bone tumors and the conditions which simulate or accompany them," and no wonder, since your surgical boards accept recognition of a set number of histological preparations as knowledge of pathology—they fail to realise that the variations in histopathological material are infinite and that this has resulted (and still does result) in as many variations in interpretation as the number of eminent pathologists to whom identical preparations are submitted. Comparisons are odious. It is not my fault that Dr. Macdonald has been so unfortunate in his experience with interpretation of radiographs showing metastases. I have done my best to disseminate knowledge.

The surgeon who contemplates doing a biopsy and who fails first to undertake to abide by the pathologist's report, even if this means amputation or serious mutilation, and to ascertain if the latter would be permitted, inflicts unjustifiable assault on his patient. Only too frequently he fails to consider what he will do if the pathologist reports malignant disease; in spite of the report, he often acts contrary to its dictates or finds that the patient or parents forbid his surgery.

Instead of doing a biopsy, if the lesion is localized and calls for surgery, why not resect it in its entirety at the first operation? The whole lesion can be submitted to the pathologist and if the latter reports it to be benign—even though this may prove to be wrong—useful surgery has been done. If the pathologist reports it as malignant, the surgeon can be thankful that he did his best to remove it all; he can then await events or, if he is convinced, and considers it expedient, proceed to amputation. I have known many such localised resections to result in cure, though histological examinations of the resected lesions were interpreted as malignant.

One eminent pathologist, whose general work I much admire, said he believed so much in the value of the radiograph that he would not report on the histology of a bone lesion until he had carefully examined the radiographs. This I regard as an important admission of the lack of confidence in histology. I would not allow histopathology to bias my interpretation of the radiograph for the same reason, and I have no respect for an interpretation of histology which is biased by radiographic appearances.

Let it be clearly understood that my criticisms of biopsy are confined to bone lesions—radiology cannot compete with histopathology in lesions of soft tissues.

Finally, may I take this opportunity of thanking the radiologists of your great country for the kindness and hospitality which they have so charmingly bestowed throughout my tour—in particular the younger men who have so stimulated my efforts.

Yours sincerely,

JAMES F. BRAILSFORD, M.D., F.R.C.P.

Books Received

Books received are acknowledged under this heading and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

L'URETHROGRAPHIE. By ROGER GUICHARD, Radiologist, Hospitals of Bordeaux, and HENRY DUVERGEY, Chief of Urologic Clinic of the Faculty of Bordeaux, with a Preface by PROFESSOR DARGET. A volume of 190 pages, with 165 figures. Published by Masson & Cie, Paris, 1948.

AN ATLAS OF MYELOGRAPHY. Prepared for the Registry of Radiologic Pathology, American Registry of Pathology, National Research Council, from Material in the Files of the Neurological Institute of New York. By ERNEST H. WOOD, JR., M.D., Assistant Professor of Radiology in the College of Physicians and Surgeons, Columbia University; Assistant Attending Radiologist to the Presbyterian Hospital in the City of New York. A volume of 114 pages, with 42 figures. Published by Registry Press, Washington, D. C., 1948. Price $5.00.

ISOTOPIC CARBON. TECHNIQUES IN ITS MEASUREMENT AND CHEMICAL MANIPULATION. By MELVIN CALVIN, Professor of Chemistry, CHARLES HEIDELBERGER, JAMES C. REID, BERT M. TOLBERT, and PETER F. YANKWICH, Instructors in Chemistry. All Members of the Scientific Staff of the Radiation Laboratory, University of California, Berkeley. A volume of 376 pages, with 107 figures. Published by John Wiley & Sons, Inc., New York; Chapman & Hall, Ltd., London, 1949. Price $5.50.

NEURORADIOLOGY. By ALEXANDER ORLEY, M.D., F.F.R., D.M.R. & E., Hon. Consulting Radiologist, West End Hospital for Nervous Diseases, London. A volume of 422 pages, with 572 illustrations. Published by Charles C Thomas, Springfield, Ill., 1949. (In England by Blackwell Scientific Publications, Ltd., Oxford. In Canada by the Ryerson Press, Toronto.) Price $11.50.

Book Reviews

ARTHRITIS AND RELATED CONDITIONS. Edited by THEODORE FRANKLIN BACH, M.D., F.A.C.P., Assistant Professor of Medicine in the Graduate School of Medicine of the University of Pennsylvania, Philadelphia; Chief of Arthritic Clinic, Abington Memorial Hospital, Abington, Penna. A volume of 452 pages, with 146 illustrations. Published by F. A. Davis Co., Philadelphia, 1948. Price $6.50.

The plans and production of this book on Arthritis and Related Conditions were first organized by Dr. R. Garfield Snyder, whose untimely death cut short his careful planning for its publication. The publisher, at the suggestion of Dr. George Morris Piersol, asked Dr. Theodore Franklin Bach to re-evaluate and complete the task.

In addition to the work of Drs. Snyder and Bach, contributions were made by Irving Balensweig, M.D., William Bates, M.D., J. Borak, M.D., Edith H. Brokaw, O.T.R., K. G. Hansson, M.D., Arthur Krida, M.D., John C. McCauley, Jr., M.D., Dudley J. Morton, M.D., and C. H. Traeger, M.D., each of whom is a specialist in his own field.

Though written primarily for the general practitioner, the book gives to the radiologist the advantage of knowing what is of special interest to the physician in managing arthritis, in association with or independent of radiology.

The book includes twenty-eight chapters; fourteen of the last eighteen have been written by the authors named above, who are interested in particular phases of the disease, but especially in its therapy. The broad view taken by the editor, Dr. Bach, regarding arthritis is due surely in part to his association with Dr. Ralph Pemberton, one of our greatest rheumatologists. This view is illustrated by his statement regarding the treatment of rheumatoid arthritis in Chapter IX: "Since we are dealing with a disease of unknown etiology, the treatment cannot be stereotyped."

Of special interest radiologically are Chapters XIII and XIV, written by J. Borak, M.D. For eight years, Dr. Borak was Director of the Department of X-ray Therapy in the Institute of Dr. Guido Holzknecht in Vienna. Subsequently he served for eight years as Director of the radiological department in the Rothschild Hospital in Vienna, where x-rays came to be considered an essential in the treatment of arthritis, as they have long been recognized to be in the fields of tumors and skin diseases. During recent years, he has been doing x-ray therapy in arthritic conditions in the Clinic of the Medical College of New York University and in the Goldwater Memorial Hospital, New York City.

Borak discusses in detail the pathological conditions in the tissues involved in arthritis, and then, under "Principles of X-ray Therapy," indicates the variations in the technic that are necessary to adapt the radiological effects to the pathological conditions that are present in the particular case under treatment. He indicates that the results to be obtained from roentgen therapy will vary in great part with the knowledge possessed by the radiologist regarding the conditions in the joints affected, and the skill with which he adapts his treatment to these. The principles discussed by Dr. Borak are, of course, those which are involved in any roentgen therapy. Too often failures or poor results in the past have occurred from the lack of proper technic.

In the diagnosis of the pathological conditions in arthritis, Drs. Pemberton and Bach have made special use of studies by means of the roentgen rays in the hands of various experts in Philadelphia.

In connection with the chapters on the various methods of therapy of arthritis, the most important references bearing upon the subject under discussion are listed. One is impressed, therefore, with the thoroughness with which the whole subject is treated. This book should be in every radiologist's library as well as that of every practitioner who is dealing with arthritis. The discussion by Dr. Borak seems to indicate that roentgen therapy has not been sufficiently or properly evaluated in connection with the treatment of this disease.

KREBSMETASTASEN. BY DR. HANS E. WALTHER, Chief of the Roentgen Division of the Red Cross Hospital in Zürich, with a foreword by PROF. DR. H. VON MEYENBURG, Director of the Pathological Institute in Zürich. A volume of 560 pages, with 359 illustrations. Published by Benno Schwabe & Co., Basel, Switzerland. Imported by Grune & Stratton, Inc., New York.

It is unusual that a radiologist can write a book on metastatic carcinoma based not only on a very extensive experience gained by clinical work, but

mainly on an evaluation of a large autopsy series. Dr. Walther has made use of a material comprising 3,433 autopsies of cancer cases seen during the course of many years in the Pathological Institute of the City of Zurich to try to clear up some of the many divergencies between the point of view of the anatomist, physiologist, and pathologist on the one side and the clinician and radiologist on the other side.

By very careful postmortem technic, with special consideration of the relationship of the primary cancer and its metastases, many interesting conclusions have been reached. Definite types of localization of metastases were demonstrated. The method of distribution of metastases follows the physiological laws of the circulatory system, be it lymphatic or vascular. The lungs and the liver take over the role of primary or secondary filters. The author was able to prove his hypothesis by the fact that with correct technic such metastatic foci could almost always be found when expected in a certain type of cancer. He is of the opinion that secondary cancerous foci in the lungs are always the place of origin for metastases taking place through the arterial circulation. These lung metastases are often very small and easily missed even at autopsy. The degree and extent of further metastases originating from the lungs is in no way related to their size.

The author's ideas about lymphatic metastases are in many ways contrary to accepted teaching. Metastatic lymph-node involvement is always regional. It may be primary if caused by the primary tumor or secondary if caused by a metastasis in another organ.

In the second part of the book the different types of cancer of the different organs are dealt with. A clear and concise index of malignancy is given for the various types of tumors originating in the different parts of the body. It is based on the frequency of occurrence, the tendency to infiltrate surrounding tissue, and the type and extent of metastases. All these conclusions are reached by means of extensive and comprehensive tables and percentages based upon careful pathological-anatomical investigations. Many excellent illustrations of gross and microscopic specimens and some roentgenograms serve to illustrate the different types of tumors and their metastases.

There is no question that this book is the most extensive and careful study which the problem of cancer metastasis has ever received. It probably will be a standard textbook in this field for a long time to come. Every physician who deals with cancer will find it a most important addition to his library. Each chapter has a fairly inclusive bibliography of European and American literature.

In Memoriam

DR. GORDON EARLE RICHARDS

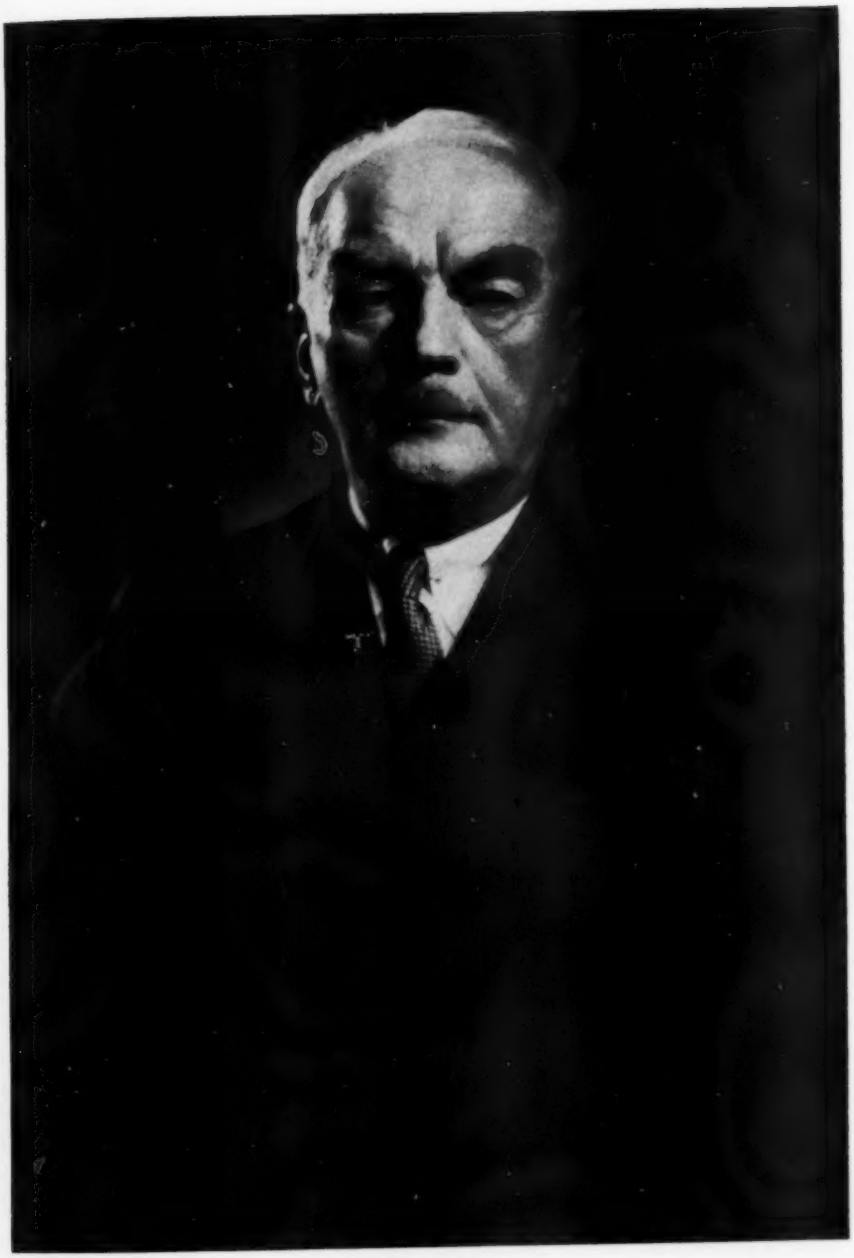
Dr. Gordon Earle Richards, Canadian radiologist of international renown, died in the Toronto General Hospital on Jan. 13, 1949, at the age of sixty-three.

For the greater part of his medical career Dr. Richards concentrated all his knowledge, skill, and experience on the treatment of cancer by x-rays and radium. In this field his success was outstanding, making him a leader in radiotherapeutics, respected and consulted by his fellow specialists. His high reputation as an authority on cancer inspired the invitation from London, England, to deliver the Skinner Lecture on cancer there, in 1947. This was the first occasion since the inauguration of that lectureship that any specialist outside Europe was so honored. Dr. Richards was original and thorough in his methods, earned the confidence and respect of thousands of patients, and never spared himself through many years of exacting examinations, consultations, and the supervision or personal administration of unnumbered treatments. His interest and activity never lagged, and the grand ideal of his life, greater achievements in the conquest of cancer, was constantly before him.

Gordon E. Richards, M.B. (Tor.), L.L.D., F.R.C.P. (C), F.A.C.R., and Honorary Member of the Royal Society of Medicine, England, was born at Lyn, Ontario, in 1885. He was the son of the Reverend J. J. Richards and Anna Paul Richards. His preliminary education was in the public school of Lyn and the Athens, Ontario, high school. He was graduated in medicine from the University of Toronto in 1908, as gold-medallist. Postgraduate studies in Europe included Frankfurt, Germany, with Professors Dessauer and Holfelder, and later work in London, Paris, and Stockholm. British Columbia was the scene of his first practice. During the First World War he was radiologist to No. 21 General Hospital of the R.A.M.C. and saw service during the Dardanelles Campaign on Lemnos and at Alexandria, Egypt. In the second world conflict he conducted a training school for radiologists in Toronto for the R.C.A.M.C. and the R.C.A.F.

Appointed the first radiologist at Toronto General Hospital in 1917, his zeal and efficiency developed the department of radiology there to one of the foremost in North America. In 1920 he introduced the first high-voltage x-ray machine for therapeutic service into Canada. In 1937 he was instrumental in founding the Canadian Association of Radiologists, now a society comprising more than 90 per cent of Canadian radiologists. From 1916 to 1948 his contributions to medical and radiological literature grew into a lengthy bibliography.

Dr. Richards held many appointments of great responsibility. He was Director of the Ontario Institute of Radiotherapy; Managing Director of



Gordon E. Richards, M.D.
1885–1949

Curtis Biltmore Studios, Los Angeles

Henry Snure, M.D.
1887–1948

the Ontario Cancer Treatment and Research Foundation; Attending Radiologist-in-Chief, Toronto General Hospital, and Professor of Radiology at the University of Toronto. He was a member of the Toronto Academy of Medicine, the Ontario and Canadian Medical Associations, the Radiological Society of North America, and the American Roentgen Ray Society.

As the citation delivered at Queen's University in 1947, when he was honored with the degree of Doctor of Laws, said in part, he was "—a foremost Canadian scientist in cancer radiotherapy, internationally known as teacher, researcher, administrator; greatly serving mankind." He was a radiologist of renown, and a great Canadian.

ARTHUR C. SINGLETON, M.D.

DR. HENRY SNURE

Dr. Henry Snure, of Los Angeles, died in May 1948, of cerebral hemorrhage, the culmination of a long-standing hypertension.

Dr. Snure was born at Lakefield, Minnesota, in November 1887, and had his preliminary education at Concordia College, St. Paul, Minnesota. He was graduated from the University of Louisville Medical School in 1910, and practised in Ohio, Missouri, North Dakota, and Michigan until 1916, at which time he went to California. During World War I, he was in active service, stationed at Mare Island.

Dr. Snure was radiologist for St. Vincent's Hospital in Los Angeles from 1916 to 1921. During the following eleven years he served as radiologist at the California Hospital. He was a Councilor for the Los Angeles County Medical Association from 1925 to 1926, and again from 1930 to 1934. He was a member of the Radiological Society of North America, the American Roentgen Ray Society, and the American College of Radiology, and a diplomate of the American Board of Radiology.

A conscientious and painstaking physician, Dr. Snure often carried far more than his share of the load. He is greatly missed by his associates.

WILBUR BAILEY, M.D.

RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

Editor's Note: Secretaries of state and local radiological societies are requested to co-operate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates.

UNITED STATES

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 713 E. Genesee St., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Hugh F. Hare, M.D., 605 Commonwealth Ave., Boston 15, Mass.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Harold Dabney Kerr, M.D., Iowa City, Iowa.

AMERICAN COLLEGE OF RADIOLOGY. *Secretary*, William C. Stronach, 20 N. Wacker Dr., Chicago 6, Ill.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, U. V. Portmann, M.D., Cleveland Clinic, Cleveland 6, Ohio.

Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, W. D. Anderson, M.D., 2501 6th St., Tuscaloosa.

Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and at meeting of State Medical Society.

California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, Sydney F. Thomas, M.D., Palo Alto Clinic, Palo Alto.

LOS ANGELES RADIOLOGICAL SOCIETY. *Secretary*, Wybren Hiemstra, 1414 S. Hope St., Los Angeles 15. Meets second Wednesday of each month at County Society Bldg.

NORTHERN CALIFORNIA RADIOLOGICAL CLUB. *Secretary*, Charles E. Grayson, M.D., Medico-Dental Bldg., Sacramento 14. Meets at dinner last Monday of September, November, January, March, and May.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually with State Medical Association.

SAN DIEGO ROENTGEN SOCIETY. *Secretary*, R. F. Niehaus, M.D., 1831 Fourth Ave., San Diego. Meets first Wednesday of each month.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Ivan J. Miller, M.D., 49 Fourth St. Meets monthly on the third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Langley Porter Clinic, University of California Hospital.

Colorado

COLORADO RADIOLOGICAL SOCIETY. *Secretary*, Mark S. Donovan, M.D., 306 Majestic Bldg., Denver 2. Meets third Friday of each month, at the Colorado School of Medicine and Hospitals.

Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Robert M. Lowman, M.D., Grace-New Haven Hospital, Grace Unit, New Haven. Meetings bimonthly, second Thursday.

CONNECTICUT VALLEY RADIOLOGIC SOCIETY. *Secretary*, Ellwood W. Godfrey, M.D., 1676 Boulevard, W. Hartford. Meets second Friday of October and April.

District of Columbia

RADIOLOGICAL SECTION, DISTRICT OF COLUMBIA MEDICAL SOCIETY. *Secretary*, Alfred A. J. Den, M.D., 1801 K St., N.W., Washington 6. Meets third Thursday, January, March, May, and October, at 8:00 P.M., in Medical Society Auditorium.

Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, F. K. Hurt, M.D., Riverside Hospital, Jacksonville. Meets in April and in November.

Georgia

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert Drane, M.D., De Renne Apartments, Savannah. Meets in November and at the annual meeting of State Medical Association.

Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, T. J. Wachowski, M.D., 310 Ellis Ave., Wheaton. Meets at the Palmer House, second Thursday of October, November, January, February, March, and April, at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William DeHollander, M.D., St. Johns' Hospital, Springfield. Meetings quarterly as announced.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Harold L. Shinall, M.D., St. Joseph's Hospital, Bloomington.

Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, William M. Loehr, M.D., 712 Hume-Mansur Bldg., Indianapolis 4. Annual meeting in May.

Iowa

IOWA X-RAY CLUB. *Secretary*, Arthur W. Erskine, M.D., 326 Higley Building, Cedar Rapids. Meets during annual session of State Medical Society.

Kansas

KANSAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Anthony F. Rossitto, M.D., Wichita Hospital, Wichita. Meets annually with State Medical Society.

Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Everett L. Pirkey, M.D., 323 East Chestnut St., Louisville 2.

LOUISVILLE RADIOLOGICAL SOCIETY, *Secretary-Treasurer*, Everett L. Pirkey, Louisville General Hospital, Louisville 2. Meets second Friday of each month at Louisville General Hospital.

Louisiana

LOUISIANA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Johnson R. Anderson, M.D., No. Louisiana Sanitarium, Shreveport. Meets with State Medical Society.

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets first Tuesday of each month.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, Oscar O. Jones, M.D., 2622 Greenwood Road. Meets monthly September to May, third Wednesday.

Maryland

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, J. Howard Franz, M.D., 1127 St. Paul St., Baltimore 2.

Michigan

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary-Treasurer*, George Belanger, M.D., Harper Hospital, Detroit 1. Meetings first Thursday, October to May, at Wayne County Medical Society club rooms.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *Secretary-Treasurer*, R. B. MacDuff, M.D., 220 Genesee Bank Building, Flint 3.

Minnesota

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, C. N. Borman, M.D., 802 Medical Arts Bldg., Minneapolis 2. Meets in Spring and Fall.

Missouri

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, Wm. M. Kitchen, M.D., 1010 Rialto Building, Kansas City 6, Mo. Meetings last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Edwin C. Ernst, M.D., 100 Beaumont Medical Bldg. Meets on fourth Wednesday, October to May.

Nebraska

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Ralph C. Moore, M.D., Nebraska Methodist Hospital, Omaha 3. Meets third Wednesday of each month at 6 P.M. in Omaha or Lincoln.

New England

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, George Levene, M.D., Massachusetts Memorial Hospitals, Boston. Meets monthly on third Friday at Boston Medical Library.

New Hampshire

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary-Treasurer*, Albert C. Johnston, M.D., Elliot Community Hospital, Keene. Meetings quarterly in Concord.

New Jersey

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Raphael Pomeranz, M.D., 31 Lincoln Park, Newark 2. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark.

New York

ASSOCIATED RADIOLOGISTS OF NEW YORK, INC. *Secretary*, William J. Francis, M.D., East Rockaway.

BROOKLYN ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Abraham H. Levy, M.D., 1354 Carroll St., Bklyn. 13. Meets fourth Tuesday of each month, October to April.

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*. Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meetings second Monday, October to May.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary-Treasurer*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 10. Meetings in January, May, and October.

LONG ISLAND RADIOLOGICAL SOCIETY. *Secretary*, Marcus Wiener, M.D., 1430 48th St., Brooklyn 19. Meetings fourth Thursday evening, October to May, at 8:45 P.M., in Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Wm. Snow, M.D., 941 Park Ave., New York 28.

QUEENS ROENTGEN RAY SOCIETY. *Secretary*, Jacob E. Goldstein, M.D., 88-29 163rd St., Jamaica 3. Meets fourth Monday of each month.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary-Treasurer*, Ralph E. Alexander, M.D., 101 Medical Arts Bldg., Rochester 7. Meets at Strong Memorial Hospital, third Monday, September through May.

North Carolina

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary-Treasurer*, James E. Hemphill, M.D., Professional Bldg., Charlotte 2. Meets in May and October.

North Dakota

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary*, Charles Heilman, M.D., 1338 Second St., N., Fargo.

Ohio

OHIO STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Carroll Dundon, M.D., 2065 Adelbert Road, Cleveland 6. Next meeting at annual meeting of the State Medical Association.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Paul D. Meyer, M.D., Grant Hospital, Columbus. Meets second Thursday, October, December, February, April, and June, 6:30 P.M., Seneca Hotel, Columbus.

CINCINNATI RADIOLOGICAL SOCIETY. *Secretary*, Eugene L. Saenger, M.D., 735 Doctors Bldg., Cincinnati 2. Meets last Monday, September to May.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, George L. Sackett, M.D., 10515 Carnegie Ave., Cleveland 6. Meetings at 6:30 P.M. on fourth Monday, October to April, inclusive.

Oklahoma

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, W. E. Brown, M.D., 21st and Xanthus, Tulsa 4. Meets in October, January, and May.

Oregon

OREGON RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Boyd Isenhart, M.D., 214 Medical-Dental Bldg., Portland 5. Meets monthly, on the second Wednesday, at 8:00 P.M., in the library of the University of Oregon Medical School.

Pacific Northwest

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney J. Hawley, M.D., 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Arthur Finkelstein, M.D., Graduate Hospital, Philadelphia. Meets first Thursday of each month at 8:00 P.M., from October to May, in Thomson Hall, College of Physicians, 21 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, R. P. Meader, M.D., 4002 Jenkins Arcade, Pittsburgh 22. Meets second Wednesday of each month at 6:30 P.M., October to June.

Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maurice D. Frazer, M.D., Lincoln Clinic, Lincoln, Nebr. Next meeting in Denver, Colo., Aug. 18–20, 1949.

South Carolina

SOUTH CAROLINA X-RAY SOCIETY. *Secretary-Treasurer*, Robert B. Taft, M.D., 103 Rutledge Ave., Charleston 16.

South Dakota

RADIOLOGICAL SOCIETY OF SOUTH DAKOTA. *Secretary-Treasurer* Marianne Wallis, M.D., 1200 E. Fifth Ave., Mitchell. Meets during Annual Session of State Medical Society.

Tennessee

MEMPHIS ROENTGEN CLUB. Meetings second Tuesday of each month at University Center.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frére, M.D., 707 Walnut St., Chattanooga. Meets annually with State Medical Society in April.

Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, X. R. Hyde, M.D., Medical Arts Bldg., Fort Worth 2. Meetings on third Monday of each month in Dallas in the odd months and in Fort Worth in the even months.

HOUSTON X-RAY CLUB. *Secretary*, Curtis H. Burge, M.D., 3020 San Jacinto, Houston 4. Meetings fourth Monday of each month.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth.

Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Angus K. Wilson, M.D., 343 S. Main St., Salt Lake City. Meets third Wednesday, January, March, May, September, November.

Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, P. B. Parsons, M.D., Norfolk General Hospital, Norfolk 7.

Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Homer V. Hartzell, M.D., 310 Stimson Bldg., Seattle 1. Meetings fourth Monday, October through May, at College Club, Seattle.

Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Theodore J. Pfeffer, M.D., 839 N. Marshall St., Milwaukee 2. Meets monthly on second Monday at the University Club.

RADIOLOGICAL SECTION OF THE WISCONSIN STATE MEDICAL SOCIETY. *Secretary*, S. R. Beatty, M.D., 185 Hazel St., Oshkosh. Two-day meeting in May; one-day with State Medical Society, September.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursdays 4 P.M., September to May, Service Memorial Institute, Madison 6.

Puerto Rico

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA. *Secretary*, Jesús Rivera Otero, M.D., Box 3542, Santurce, Puerto Rico.

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, E. M. Crawford, M.D., 2100 Marlowe Ave., Montreal 28, Quebec. Meetings in January and June.

LA SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origéne Dufresne, M.D., Institut du Radium, Montreal. Meets third Saturday each month.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. Offices in Hospital Mercedes, Havana. Meets monthly.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA, *General Secretary*, Dr. Dionisio Pérez Cosío Marsella 11, México, D. F. Meetings first Monday of each month.

ABSTRACTS OF CURRENT LITERATURE

ROENTGEN DIAGNOSIS

The Head and Neck

HADLEY, LEE A. Atlanto-Occipital Fusion, Osiculum Terminale and Occipital Vertebra as Related to Basilar Impression with Neurosurgical Symptoms 445

MCGREGOR, M. Significance of Certain Measurements of the Skull in the Diagnosis of Basilar Impression 445

OBRADOR, S. Clinical Aspects of Cerebral Cysticercosis 445

The Chest

GREER, DAVID. Diagnosis of Acute Primary Atypical Pneumonia, Etiology Unknown, in Children 445

FINLAND, MAXWELL, JOLLIFFE, LESLIE S., AND PARKER, FREDERIC, JR. Pneumonia and Erythema Multiforme Exudativum. Report of Four Cases and Three Autopsies 446

VAN WIJE, E. Rheumatic Pneumonia 446

GORDON, JOSEPH. Localization of Pulmonary Cavities by a Modified Roentgenographic Technique 446

HUANG, CHIA-SSU, AND STONE, MEI-SHIN. Tuberculosis of the Chest Wall 446

PETERSON, J. CYRIL, AND CHRISTIE, AMOS. Histoplasmosis and Pulmonary Calcifications ... 446

CASTEX, MARIANO R., AND MAZZEI, EGIDIO S. Clinical Aspects of Pulmonary Emphysema .. 447

MYERSON, RALPH M. Spontaneous Pneumothorax. A Clinical Study of One Hundred Consecutive Cases 447

BARDEN, STUART P. Important Sequelae and Complications of Hemothorax Resulting from Penetrating Wounds of the Pleural Cavity ... 447

REEVES, ROBERT J., BAYLIN, GEORGE J., AND JONES, PAUL A. Boeck's Sarcoid in Children 448

COOPER, GEORGE, JR., ARCHER, VINCENT W., AND RAPP, JOHN R. Mesothelial Mediastinal Cysts ("Pericardial Cysts."). Differential Diagnosis of Shadows Continuous with the Anterior Inferior Mediastinum 448

DIMAIO, MICHAEL. Multiple Localized Pleural Effusions as a Manifestation of Congestive Heart Failure. Report of a Case 448

THOMPSON, WILLIAM P., AND JELLEN, JOSEPH. Heart Size in Four by Five Inch Films 448

FLANCHER, L. H. Case-Finding in Iowa. Report on State-Wide Clinics and Mass X-ray Surveys 449

ISBERG, EMIL M., AND PEET, MAX M. Influence of Supradiaphragmatic Splanchnicectomy on the Heart in Hypertension 449

GROSS, ROBERT E., AND NEUHAUSER, EDWARD B. D. Compression of the Trachea by an Anomalous Innominate Artery. An Operation for Its Relief 449

ROBINSON, ARTHUR, AND HOWARD, JORGE E. Atresia of the Tricuspid Valve with Transposition of the Great Vessels 449

BAER, SAMUEL, AND LOEWENBERG, SAMUEL A. Aortic Aneurysms Simulating Organic Disease of the Gastro-Intestinal Tract 450

The Digestive System

OLSEN, ARTHUR M., AND HARRINGTON, STUART W. Esophageal Hiatal Hernias of the Short Esophagus Type: Etiologic and Therapeutic Considerations 450

MAILER, ROBERT. Carcinoma in a Thoracic Stomach (Congenital Short Œsophagus) 450

BROOKS, FRANK P., STEVENS, LLOYD W., PENDERGRASS, EUGENE P., AND BASSOLS, FRANCISCO. Experimental Studies on the Motility of the Gastric Mucosa in Dogs. A Preliminary Report 451

FRIEDMAN, MAURICE H. Peptic Ulcer and Functional Dyspepsia in the Armed Forces 451

RITVO, MAX, AND SHAUFFER, IRVING A. Roentgenographic Studies of the Gastrointestinal Tract Following Section of the Vagus Nerves for Peptic Ulcer 451

MANNING, ISAAC H., JR., AND HIGHSMITH, GEORGE P. Prolapse of the Gastric Mucosa Through the Pyloric Canal into the Duodenum. Report of 16 Cases Diagnosed Roentgenologically 451

PROBSTEIN, J. G., AND SACHAR, LEO A. Pyloric Obstruction Due to Gastric Diverticulum. Report of a Case 452

GLASS, W. H. Non-Vitaminic Factors Involved in the Production of the "Small Intestinal Deficiency Pattern" 452

DUNDON, CARROLL C. Primary Tumors of the Small Intestine 452

SINNER, B. L. Unusual Anomaly of the Gallbladder and Bile Ducts 453

BROWN, ROSWELL K., AND MILCH, ELMER. Gallbladder Gas Gangrene 453

HEIFETZ, CARL J., AND SENTURIA, H. R. Acute Pneumocholecystitis 453

KEELEY, JOHN L. Congenital Cystic Dilatation of the Common Bile Duct. Report of a Case 453

URWITZ, S. A Case of Congenital Choledochus Cyst 454

FISTER, GEORGE M., AND LUND, ANTHONY J. Pancreatic Lithiasis and Renal Lithiasis in the Same Patient 454

The Musculoskeletal System

JAFFE, HENRY L., AND LICHTENSTEIN, LOUIS. Chondromyxoid Fibroma of Bone. A Distinctive Benign Tumor Likely to be Mistaken Especially for Chondrosarcoma 454

SHACKMAN, RALPH, AND HARRISON, C. V. Occult Bone Metastases 455

BRAILSFORD, JAMES F. The Serious Limitations and Erroneous Indications in the Diagnosis of Tumours of Bone 455

REILLY, WILLIAM A., AND LINDSAY, STUART. Gargoylism (Lipochondrodystrophy). A Review of Clinical Observations in Eighteen Cases 455

KRIDELBAUGH, WILLIAM W., AND WYMAN, ALVIN C. Osgood-Schlatter's Disease 456

VAN ZEBEN, W. Infantile Cortical Hyperostoses. 456

CURR, J. F. An Osseous Dystrophy with Many Pseudo-Fractures 456

CLEVELAND, MATHER, BOSWORTH, DAVID M., AND THOMPSON, FREDERICK R. Pseudarthrosis in the Lumbosacral Spine 456

FURTADO, DIOGO, ET AL. Secondary Echinococcosis of the Vertebral Column with Possible Medullary Spread 457

SHELLITO, JOHN G., AND DOCKERTY, MALCOLM B. Cartilaginous Tumors of the Hand 457

DONALDSON, S. W., BADGLEY, CARL E., AND HUNSBERGER, W. G. Lateral View of the Pelvis in Examination for Hip Dislocation ... 457

BOST, FREDERIC C., HAGEY, HELEN, SCHOTTSTAEDT, EDWIN R., AND LARSEN, LOREN J. Results of Treatment of Congenital Dislocation of the Hip in Infancy 457

BOYD, HAROLD B., AND FOX, KERMIT W. Congenital Pseudarthrosis. Follow-Up Study After Massive Bone-Grafting 458

ROCHE, MAURICE B., AND JOSTES, FREDERIC A. Ectopic Bone Deposits. A Paraplegic Complication 458

Gynecology and Obstetrics

MORETON, ROBERT D., AND BUNKLEY, T. F. Radiology as It Relates to Obstetrics 458

SCHNEIDER, MARTIN. Roentgenologic Methods in Obstetrics 459

REUTER, E. G. Roentgen Pelvimetry 459

PARKS, JOHN, AND PUZAK, MICHAEL A. Influences of Posture on the Urinary Tract in Pregnancy 459

STALLWORTHY, JOHN. Facts and Fantasy in the Study of Female Infertility 460

The Genito-Urinary System

WOMACK, R. K., AND MATHEWS, W. R. The Renal Manifestations of Periarteritis Nodosa 460

BURNS, EDGAR, AND WHITEHEAD, C. MARK. Renal Complications of Hyperparathyroidism 460

ANTOPOL, WILLIAM, AND GOLDMAN, LESTER. Subepithelial Hemorrhage of Renal Pelvis Simulating Neoplasm 461

Technic

VALLEBONA, ALESSANDRO. Axial Stratigraphy .. 461

MACKAY, MAURICE W. H. A Viscous Diodone as a Substitute for Iodized Oil 461

RADIOTHERAPY

ACKERMAN, LAUREN V. Verrucous Carcinoma of the Oral Cavity 461

FREID, JACOB R. Roentgen Treatment of Cancer of the Esophagus 462

DEL REGATO, J. A. Rôle of Transvaginal Roentgentherapy in the Treatment of Carcinoma of the Cervix 462

DIDDLE, A. W., AND BENNETT, T. R. Carcinoma of the Cervix in an Urban Population 462

SPEERT, HAROLD. Late Recurrence of Cervical Carcinoma Following Radiation Therapy 463

FRICKE, ROBERT E., AND VARNEY, JAMES H. Peyronie's Disease and Its Treatment with Radium 463

LEWIS, LLOYD C. Testis Tumors: Report on 250 Cases 463

NIEDELMAN, MEYER L. Roentgen Ray Epilation: An Improved Measuring Device 464

RADIOACTIVE ISOTOPES

CURTISS, LEON F. Measurement of Radioactive Isotopes 464

EVANS, T. C., LENZ, M., DONLAN, C. P., AND LEMAY, M. J. Effects of Radioactive Sodium on Leukemia and Allied Diseases. Preliminary Report 464

ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Atlanto-Occipital Fusion, Ossiculum Terminale and Occipital Vertebra as Related to Basilar Impression with Neurological Symptoms. Lee A. Hadley. Am. J. Roentgenol. **59:** 511–524, April 1948.

Distortion about the foramen magnum may be due to congenital anomalies, as atlanto-occipital fusion, occipital vertebra, and ossiculum terminale, or to basilar impression secondary to softening of the base of the skull from osteitis deformans, osteogenesis imperfecta, osteomalacia, etc., producing pressure upon the cerebellum as a result of invagination of the occiput upward into the posterior fossa. The literature is concisely reviewed and a long discussion of the anatomical and embryologic features involved is presented.

The neurological manifestations of distortion of the foramen magnum may be mistaken for multiple sclerosis, spastic paralysis, amyotrophic lateral sclerosis, cerebellar or cord tumors, or syringomyelia. Strangely enough the first symptoms may not develop until the second or third decade, even though the condition is congenital. When evidence of upper cord degeneration or compression does occur, a lateral survey roentgenogram of the upper cervical spine made in full forward flexion is indicated. If the arch of the atlas is not fused to the occiput, it will separate from the bone in that position. A description of the roentgen findings in other projections is included and should be read in the original. Good stereoscopic films are considered superior to planigrams. Six cases are presented.

Twelve roentgenograms; 4 photographs; 1 drawing; 1 table.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Significance of Certain Measurements of the Skull in the Diagnosis of Basilar Impression. M. McGregor. Brit. J. Radiol. **21:** 171–181, April 1948.

After a brief review of basilar impression from the standpoint of history and etiology, the author suggests a modification of the Chamberlain line (from the dorsal lip of the foramen magnum to the dorsal margin of the hard palate) for diagnostic purposes. He suggests drawing a line from the upper surface of the posterior edge of the hard palate to the most caudal point of the occipital curve in a true lateral view. The posterior end-point of this line is more easily located than that of the Chamberlain line; the mean distance from the tip of the odontoid process to this line is more constant than to the Chamberlain line, and the standard of deviation is less.

It is also pointed out that the basal angle is not a reliable diagnostic sign of basilar impression. It may be increased or it may be normal. It is actually a measure of the relation of one part of the base to another.

Five roentgenograms; 2 drawings; 2 graphs.

SYDNEY J. HAWLEY, M.D.
Seattle, Wash.

Clinical Aspects of Cerebral Cysticercosis. S. Obrador. Arch. Neurol. & Psychiat. **59:** 457–468, April 1948.

This is a rather lengthy summary of Obrador's experience with cerebral cysticercosis during a five-year period. The locale is Mexico. His clinical classification of this condition is as follows:

1. Cortical cysticercosis
2. Ventricular cysticercosis
   (*a*) Isolated
   (*b*) Multiple
3. Basilar cysticercosis
   (*a*) Predominantly near the cisterna magna
   (*b*) Predominantly in the cerebellopontine angle
   (*c*) Predominantly in the anterior and middle cerebral fossae
4. Mixed, general, and diffuse.

The four main groups of symptoms most commonly present are epileptiform attacks, signs of increased intracranial pressure, mental disturbances, and loss of vision. The time between infection and onset of cerebral symptoms ranges from months to years.

The disease must be differentiated from other cerebral conditions, notably brain tumor, multiple sclerosis, neurosyphilis, and cortical atrophy.

The roentgenographic study of the skull shows two main types of change: the *non-specific* type, with the usual signs of increased intracranial pressure, and the specific type, consisting in multiple, small, diffuse, intracranial calcifications, seen in over a third of the cases. More rarely, the cysts produce areas of erosion of bone in the cranial vault. Air studies may be of aid. There is often dilatation of the lateral ventricles, symmetrical or asymmetrical. There may be rather considerable cortical atrophy. The association of hydrocephalus and diffuse cerebral atrophy is considered fairly typical of cerebral cysticercosis.

The cerebrospinal fluid shows non-specific inflammatory changes, which are of no definite aid to diagnosis. There may be a cerebrospinal fluid eosinophilia. The specific reaction to the complement-fixation test is believed by the authors to be an important and specific observation.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

THE CHEST

Diagnosis of Acute Primary Atypical Pneumonia, Etiology Unknown, in Children. David Greer. Texas State J. Med. **43:** 771–775, April 1948.

The author introduces this article with the statement: "If a conclusion were to be based on pediatric literature, it would appear that little attention has been given to the occurrence of acute primary atypical pneumonia, etiology unknown, in children." This type of pneumonia he definitely differentiates from the atypical pneumonias ascribed to the viruses of the psittacosis-lymphogranuloma or ornithosis group, those complicating brucellosis, measles, lymphocytic choriomeningitis, and influenza, certain rickettsial infections, and such conditions as toxoplasmosis, coccidioidosis, and other mycotic diseases, as well as the so-called eosinophilic pneumonia. He himself observed 66 cases in patients below fifteen years of age in a period of some three years. The incidence was greatest in spring and early summer.

The symptoms, blood findings, and roentgen observations in these young patients are discussed.

The first roentgen changes noted are increased density of the hilar and usually the perihilar shadows in the affected area, with soft lace-like infiltration along the radiating bronchovascular structures, which, however, are seldom completely obscured. The infiltration may extend outward, fanwise, or may take a roughly pyramidal form with the base at the hilum. In a minority of cases the pulmonary infiltration departs from these more typical forms, appearing as a diffuse finely nodular mottling that may extend throughout all of one or more lobes. Such cases may be confused with certain forms of the invasive stage of early childhood tuberculosis or coccidioidomycosis. The location of the lesions in children was found to correspond with that in the young adult, the lower lobes being predominantly involved.

Differential diagnosis must take into consideration, beside tuberculosis and coccidioidomycosis, already mentioned, bronchopneumonias of bacterial origin and so-called allergic pneumonia.

In closing, the author points out that in his experience primary atypical pneumonia ranks second only to infectious mononucleosis in the ease and probable frequency with which it may be overlooked. He points out that a primary atypical pneumonia may accompany or complicate any acute febrile illness of childhood of known bacteriological origin.

Four roentgenograms; 4 tables.

S. F. THOMAS, M.D.
Palo Alto, Calif.

Pneumonia and Erythema Multiforme Exudativum. Report of Four Cases and Three Autopsies. Maxwell Finland, Leslie S. Jolliffe, and Frederic Parker, Jr. Am. J. Med. **4:** 473–492, April 1948.

Four cases of erythema multiforme exudativum are reported; 3 of them were fatal, and the autopsy findings are presented. There was a diffuse miliary type of pneumonia in 2 of the patients who died and the one who recovered. The pneumonia in these patients resembled the severe and diffuse primary atypical pneumonia of unknown etiology in every respect—clinically, roentgenographically, and pathologically; it resembled psittacosis pneumonia in many ways. In one of the fatal cases there was a significant amount of secondary bacterial infection.

Evidence suggesting a possible infection with a psittacosis-like virus was obtained in 3 cases. In Case 1 there was a significantly high titer of antibody for psittacosis virus demonstrated by complement fixation. In Case 2 there was a significant rise in titer of such antibodies during the course of the illness and a history of contact with a dead pigeon eight days before the first symptom. In Case 4 there was only a history of contact with a sparrow during its fatal illness. This patient died on the fifth day of his disease and the lungs showed only a few focal lesions in the alveolar walls. No virus was isolated from any of the patients.

Cold agglutinins were demonstrated in high titer in the serum of 1 patient and appeared during the course of the illness in 2 others.

Five roentgenograms; 11 photographs; 9 photomicrographs; 3 charts.

Rheumatic Pneumonia. E. van Wijk. Acta paediat. **35:** 108–116, 1948.

Three cases of acute rheumatism and pneumonia in children are reported. Two of the children had rheumatic manifestations and pneumonia simultaneously, while in the third patient the rheumatic symptoms developed after a pulmonary inflammation which did not respond to chemotherapy. The author reviews the literature and discusses the reasons for the diagnosis of rheumatic pneumonia and the treatment in such cases.

Localization of Pulmonary Cavities by a Modified Roentgenographic Technique. Joseph Gordon. J. Thoracic Surg. **17:** 274–279, April 1948.

The author feels that pulmonary cavities can be more accurately localized roentgenographically if the central ray passes through the center of the cavity. This is achieved by locating the cavity fluoroscopically and taking spot films with the central fluoroscopic beam. A still more accurate localization is obtained by marking the skin directly over the cavity, anteriorly and posteriorly, during fluoroscopy and then taking 72-inch films centering on the skin marks. If the cavity is located posteriorly, the film should be made in the anteroposterior position and *vice versa*.

The maximum shift in the location of the cavity when the films are centered properly as compared with the conventional method was a little more than the width of one rib posteriorly. This does not seem to be enough of a difference to warrant any special technic.

Fourteen roentgenograms.

HAROLD O. PETERSON, M.D.
University of Minnesota

Tuberculosis of the Chest Wall. Chia-Ssu Huang and Mei-Shin Stone. Chinese M. J. **66:** 125–129, March 1948.

Tuberculous infection of the chest wall may result from direct extension of pulmonary or pleural tuberculosis *via* the lymphatics. Eight cases are here recorded with the results of radical operation. Four cases were cured and 2 improved with probability of ultimate cure. Roentgenograms may show the shadow of the abscess or destructive changes in bone. Absence of roentgen evidence, however, does not necessarily rule out this condition, as cartilage does not usually cast any shadow. In 4 of the cases in the present series a correct roentgen diagnosis was made. In 1 case, roentgenography failed to show the lesion in the rib as later revealed by operation. In another case, there was suggestive evidence of tuberculosis of the sternum on x-ray films but it was not verified at the time of operation. In the remaining 2 cases, roentgenograms did not show the correct sites of the lesions.

Histoplasmosis and Pulmonary Calcifications. J. Cyril Peterson and Amos Christie. Am. Rev. Tuberc. **57:** 361–366, April 1948.

The authors discuss the significant features of the relation of histoplasmin sensitivity to pulmonary calcification and review the preliminary evidence which favors the existence of benign forms of histoplasmosis. Studies from numerous areas show that pulmonary calcifications are statistically related to histoplasmin sensitivity and that such calcifications are much more prevalent in communities where histoplasmin sensitivity is highly prevalent than in regions of low prevalence. All observers have found an increasing percentage of reactors to histoplasmin in childhood with increasing years.

Calcifications in individuals with histoplasmin

sensitivity were found to be qualitatively different from those occurring with tuberculin sensitivity. The former lesions were often massive, multiple, and there were excessive instances of miliary calcification. It is emphasized that most individuals with positive skin test shave no known history of any illness preceding the change from a negative to a positive test. On the other hand, in the majority of fulminating infections the patients have not reacted to known potent antigens. This fact is accepted as indicating a form of anergy resulting from an overwhelming infection, the counterpart of which is well known in tuberculosis. The histoplasmin test cannot, therefore, be used in all illnesses to exclude the possibility of histoplasmosis.

L. W. PAUL, M.D.
University of Wisconsin

Clinical Aspects of Pulmonary Emphysema. Mariano R. Castex and Egidio S. Mazzei. J. franç. de méd. et chir. thoraciques **2:** 19–53, 1948. (In French.)

The clinical aspects of pulmonary emphysema are completely covered in this excellent 34-page monograph by Castex and Mazzei of Buenos Aires. An extensive bibliography is included. The subject is treated under seven headings.

(*1*) *Classic bronchogenic emphysema,* which is so frequently associated with bronchial processes, bronchitis, asthma, etc., is the most clinically apparent type. It is to be differentiated from chronic pulmonary insufflation (see below).

(*2*) *Chronic pulmonary insufflation,* or functional alveolar distention, is associated with bronchial processes which are frequently spastic. While bronchogenic emphysema constitutes an irreversible process with the anatomic characteristics of loss of elasticity, atrophy, dilatation of alveoli, ischemia, and rupture of alveolar walls, chronic alveolar insufflation is a functional, reversible state. This reversibility is shown by the improvement which results when asthma or spastic bronchitis is successfully treated.

Clinically, it is more common to find this insufflation associated with bronchogenic emphysema, and the former can be considered responsible for periods of exacerbation of symptoms such as dyspnea and cyanosis.

Aside from chronic bilateral alveolar insufflation, unilateral, monolobar, and monozonal alveolar insufflation also occur; these are symptomatic of processes which incompletely obstruct the bronchi.

(*3*) *Bronchogenic emphysema of the "black cardiacs" (Ayerza's disease).*

(*4*) *Thoracogenic emphysema:* Cases of emphysema in which a coincident bronchopathy is not found are usually spoken of as essential or diathesic emphysema. Investigations of recent years indicate that this type of emphysema is thoracogenic in origin. The primary disease is found usually not in the lungs but in the thoracic cage or vertebral column, which explains why this type of emphysema is more frequently found in patients over forty or fifty years of age, the period when degenerative diseases of the cord are more frequent.

(*5*) *Experimental Emphysema:* The authors were able to prove experimentally (in dogs) that bronchogenic emphysema develops in three stages: (*a*) alveolar insufflation, (*b*) anatomic emphysema, and (*c*) bullous emphysema. They were also able to demonstrate the effect of emphysema on the right ventricle.

(*6*) *Giant bullous emphysema.* The final state of obstructive emphysema may be the formation of giant bullae, which can occupy the entire hemithorax. These bullae have often been confused with congenital malformations, and some authorities believe that the majority of so-called "cystic diseases" of the lung are in reality acquired lesions.

(*7*) *Bullous emphysema due to pulmonary cancer:* A ball-valve mechanism created by bronchogenic carcinoma may lead to emphysema. Three possible stages may be seen: (*a*) pulmonary insufflation or emphysema, which can subsequently be replaced by total bronchial obstruction and atelectasis; (*b*) pulmonary insufflation, which maintains itself and leads to bullous emphysema of the entire bronchial sector; (*c*) insufflation and bullous emphysema complicated by spontaneous pneumothorax.

Eight roentgenograms; 5 photomicrographs; 1 electrocardiogram; 2 tables.

RODERICK L. TONDREAU, M.D.
The Mayo Clinic

Spontaneous Pneumothorax. A Clinical Study of One Hundred Consecutive Cases. Ralph M. Myerson. New England J. Med. **238:** 461–463, April 1, 1948.

This is a study of 100 consecutive unselected cases of spontaneous pneumothorax from the Boston City Hospital seen between 1934 and 1943. The diagnosis was made on the history, physical signs, and x-ray findings.

The patients are divided into two groups. In the first, numbering 64, underlying pulmonary disease was known to be present; the second consisted of 36 apparently healthy persons. The history and physical findings in the two groups are essentially the same. Eighty per cent of the cases occurred without excessive activity, while 20 per cent followed unusual exertion. Chest pain always occurred, localized to the involved side. Dyspnea was also a constant finding, being more subjective than objective, however. Cough and fever were common. Physical signs varied with the degree of collapse; with 40 per cent pneumothorax the classical signs were present.

Of the 64 patients with underlying disease, 38 had tuberculosis, 5 emphysema, 5 bronchiectasis, 4 postpneumonic emphysema, 3 bronchial asthma, 3 lung abscess, 2 metastatic carcinoma, 2 pneumonia, 1 bronchogenic carcinoma, and 1 pulmonary infarct. The average age for this group was forty-six years. The occurrence of spontaneous pneumothorax in patients over forty-five years should make one suspect underlying pulmonary disease.

Of the 36 apparently normal persons, 83 per cent were males. In 3 patients the condition was recurrent. The average age of this group was twenty-seven years. In only one instance is pulmonary tuberculosis known to have developed.

Two tables.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Important Sequelae and Complications of Hemothorax Resulting from Penetrating Wounds of the Pleural Cavity. Stuart P. Barden. Am. J. Roentgenol. **59:** 525–532, April 1948.

Bleeding into the pleural cavity is the most important complication of thoracic injuries to be dealt with in these days of sulfa and antibiotics. The author states at the onset that one important lesson of World War II is that prompt and repeated aspiration is the immediate

treatment of choice. Satisfactory resolution of a hemothorax and re-expansion of an associated pneumothorax may be obtained by simple thoracentesis if bleeding ceases promptly. With continued slow bleeding, however, if the blood begins to organize before it can be evacuated, thick layers of fibrin are deposited on the pleura. In the presence of an associated pneumothorax this interferes with respiratory exchange and prevents expansion of the partially or completely collapsed lung. The result is often a semiloculated hemopneumothorax with a dead space which can be obliterated only by radical surgical decortication of the thick, tough, leathery fibrinous pleuritis. Should the fibrinous pleuritis be of only moderate degree, and not contribute to an irreversible pneumothorax, spontaneous clearing may occur.

Six cases representative of the various clinical courses that may follow the presence of free blood in the pleural cavity are reported.

Thirty-three roentgenograms.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Boeck's Sarcoid in Children. Robert J. Reeves, George J. Baylin, and Paul A. Jones. South. M. J. **41:** 295–302, April 1948.

The occurrence of Boeck's sarcoid in children is not as rare as formerly believed. A series of 13 cases in patients of nine to fourteen years is here reported. Nine of the group were colored and four white. Lesions of the skin predominated in five patients, consisting mainly in a maculopapular eruption and involving chiefly the arms, legs, nose, and the region around the eyes. Iridocyclitis and corneal scarring occurred in seven cases.

Enlargement of the peripheral lymph nodes was the most prominent feature, being present in all cases. The nodes showed wide variation in size. Nine patients had mediastinal node enlargement.

Nine of the children presented parenchymal changes in the lung fields, either in the form of diffuse nodulation or patchy densities. The majority of these occurred in the patients who exhibited enlarged mediastinal nodes. Only three of the total series showed definite cyst-like changes in the phalanges.

The authors conclude that sarcoidosis in children appears the same and runs the same course as in adults. The correct diagnosis is usually reached by skin or lymph node biopsy.

Six roentgenograms; 6 photographs; 2 tables.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

Mesothelial Mediastinal Cysts ("Pericardial Cysts"). Differential Diagnosis of Shadows Continuous with the Anterior Inferior Mediastinum. George Cooper, Jr., Vincent W. Archer, and John R. Rapp. South. M. J. **41:** 285–294, April 1948.

In a series of 11 cases showing a circumscribed shadow projecting from the anterior inferior mediastinum and continuous with the shadows of the mediastinum, diaphragm, and anterior chest wall, 5 mesothelial mediastinal cysts were found. The remaining cases included a large cardiophrenic fat pad, a true lipoma, a dermoid cyst, a teratoma, a diaphragmatic hernia, and a metastatic carcinoma.

Roentgenologically, mesothelial mediastinal cysts have three consistent characteristics: (1) Their embryological development limits their occurrence to the anterior inferior mediastinum. (2) Their histologic structure is such that they cast a shadow of homogeneous density. (3) Their contour is sharply defined. The clinical picture is that produced by any slowly growing mediastinal tumor. Until compression occurs, the cysts are symptomless. When compression is present, cough, dyspnea, and pain appear. Among the conditions to be differentiated are those mentioned above, cardiac aneurysm, a unilateral sacculated pericarditis, and a primary lung tumor. Usually exploratory thoracotomy is required for a definite diagnosis. The cysts are readily removed.

The 11 case histories are presented.

Twenty roentgenograms.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

Multiple Localized Pleural Effusions as a Manifestation of Congestive Heart Failure. Report of a Case. Michael Di Maio. New England J. Med. **238:** 502–506, April 8, 1948.

This is an extensive and detailed account of a patient in severe cardiac failure who was admitted to the hospital showing marked cardiac enlargement, with all the signs and symptoms of severe congestion. A film of the chest showed the cardiac enlargement and, in addition, a localized effusion in the secondary fissure on the right, another in the upper right chest peripherally, and a third in the upper mediastinum just beneath the manubrium of the sternum. After adequate treatment, the decompensation improved and the chest cleared almost completely, with only moderate accentuation of the interlobar fissures surrounding the middle right lobe.

This case is unusual because of the multiplicity of the effusions. It was noticed that as soon as diuresis began, the shadows of effusion began to disappear.

Eight roentgenograms; 4 drawings.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Heart Size in Four by Five Inch Films. William Paul Thompson and Joseph Jellen. Am. Rev. Tuberc. **57:** 379–382, April 1948.

A method of determining heart size on 4 × 5-inch films is reported. Studies of normal individuals revealed that, on the average, the transverse diameter of the heart was 3.7 times greater in the standard than in the miniature films. This figure was accepted, therefore, as a conversion factor when comparison was made between the two technics. The transverse diameter of the heart as measured in the miniature film multiplied by the conversion factor gave the true transverse diameter of the heart, and this result then could be applied to standard prediction tables that are in general use. These tables require that height and weight of the subject be known. The authors recommend, therefore, that the height and weight be routinely recorded during mass surveys for pulmonary tuberculosis. They also believe that a diagnosis of heart disease should not be made on the basis of survey films alone, but that suspected cases should be studied clinically and with standard films. However, they are of the opinion that

some cases of heart disease will be detected as a by-product of surveys made primarily for tuberculosis.

L. W. PAUL, M.D.
University of Wisconsin

Case-Finding in Iowa. Report on State-Wide Clinics and Mass X-ray Surveys. L. H. Flancher. Am. Rev. Tuberc. **57:** 375–378, April 1948.

The tuberculosis case-finding program as employed in the state of Iowa is described. Since 1945, in addition to other lesions reported to the family physician, there has been included a report on any suspected heart condition, and the individual is asked to contact his physician for further examination. As a result of the taking of 62,714 miniature and large chest films during a ten-month period in 1946 and 1947, 926 suspected heart conditions were reported. Follow-up questionnaires sent to physicians concerning 213 of the 341 suspicious heart conditions found among high-school students showed that, in the group who reported for further examination as a result of the survey, more than half (55 per cent) proved to have definite cardiac lesions; 45 per cent were diagnosed as having no definite heart disease. It is emphasized that case-finding surveys may be of value in detecting heart disease in addition to the usual pulmonary conditions which are usually the primary consideration.

L. W. PAUL, M.D.
University of Wisconsin

Influence of Supradiaphragmatic Splanchnicectomy on the Heart in Hypertension. Emil M. Isberg and Max M. Peet. Am. Heart J. **35:** 567–583, April 1948.

Earlier studies of hypertensive patients subjected to a bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy have shown a significant improvement in abnormal electrocardiographic tracings and a definite reduction in heart size in some cases (see, for example, Peet, Woods, and Braden: J. A. M. A. **115:** 1875, 1940). To these reports there is now added a long-term study, in which all cases were followed for five years or longer. The series comprises 384 cases (no examples of malignant hypertension included). In 257 patients the presence of organic heart disease was confirmed prior to operation, electrocardiographically or by roentgenkymogram, or both; 154, or 60 per cent, of this number were alive five to twelve years after operation. In 127 patients the heart was normal, and 118 of this group, or 93 per cent, were alive after five to twelve years.

Heart size was followed by serial teleroentgenograms obtained before and after splanchnic resection. The prediction tables of P. C. Hodges and Eyster (Am. J. Roentgenol. **12:** 252, 1924. Abst. in Radiology **4:** 39, 1925) were used for frontal area determinations, and those of F. J. Hodges and Eyster (Arch. Int. Med. **37:** 707, 1926. Abst. in Radiology **7:** 304, 1926) for transverse diameters. Cardiac enlargement was present preoperatively in 177 cases, or 43 per cent of the series. Of this group, 50 per cent failed to survive five to twelve years after operation. Of those with hearts of normal size, 88.4 per cent were alive after five to twelve years.

Teleroentgenograms were recently obtained in 190 patients alive five to twelve years after operation. Of the 57 with preoperative cardiac enlargement, significant decreases in heart size were demonstrated in 25, or 44 per cent; 26, or 45.6 per cent, showed no change, and 6, or 10.4 per cent, showed a significant increase. Of the 133 hearts of normal size prior to operation, 123, or 92.5 per cent, remained unchanged and 10, or 7.5 per cent, showed an increase in size. In all cases in which a definite decrease in heart size was demonstrated, blood pressure levels were either reduced to within normal range, or a significant reduction of 15 mm. or more in diastolic pressure was maintained.

It is concluded that splanchnic resection has nothing to offer the hypertensive patient with marked cardiac enlargement. When the variation predicted is greater than 50 per cent for area or transverse diameter, the outlook is grave. The authors discuss cardiac symptoms and signs and the associated survival rates.

Twelve roentgenograms; 21 electrocardiograms; 10 tables.

HENRY K. TAYLOR, M.D.
New York, N. Y.

Compression of the Trachea by an Anomalous Innominate Artery. An Operation for Its Relief. Robert E. Gross and Edward B. D. Neuhauser. Am. J. Dis. Child. **75:** 570–574, April 1948.

This is a case report made in order to emphasize the fact that certain tracheal obstructions can be recognized by proper roentgen study and relieved by appropriate surgery. The patient was a four-month-old child with severe respiratory distress. Anteroposterior roentgenograms of the chest showed no abnormality, but in the lateral projection definite narrowing of the trachea could be seen. Iodized oil was then instilled for better visualization. A slight broadening of the trachea was apparent in the anteroposterior view, just below the thoracic inlet, while a lateral film revealed an extrinsic pressure defect on the anterior aspect of the trachea just above the level of the aortic arch, coursing obliquely upward from left to right. The defect was believed to be due to an aberrant artery arising on the left side of the aortic arch and passing obliquely in front of the trachea to its distribution on the right side. Operation showed an innominate artery which had its origin farther to the left than its normally expected position. Coursing to the right, it forcibly pressed upon the anterior and right anterolateral surfaces of the trachea, causing deformity of its structure and narrowing of the lumen. The artery was anchored forward to the sternum with silk sutures, relieving the pressure, and symptoms disappeared. Postoperative bronchograms showed great improvement in the appearance of the trachea.

One roentgenogram; 2 photographs; 1 drawing.

Atresia of the Tricuspid Valve with Transposition of the Great Vessels. Arthur Robinson and Jorge E. Howard. Am. J. Dis. Child. **75:** 575–581, April 1948.

A fatal case of atresia of the tricuspid valve is recorded in considerable detail. From a study of this case and others which have been reported, the authors conclude that atresia of the tricuspid valve can be recognized during life if its possibility is borne in mind. Of primary importance in establishing the diagnosis are the electrocardiogram and the roentgenogram. The former shows alterations in the P wave significant of enlargement of an auricle and left axis deviation. The roentgenogram reveals enlargement of the cardiac shadow, usually with absence of the pulmonary conus in the anteroposterior view. In the left anterior oblique position the absence of the cardiac shadow anterior to the aorta confirms the presence of a hypoplastic right ventricle. A mild degree of cyanosis rather than a typical morbus caeru-

leus suggests transposition of the great vessels as an associated lesion.

Five illustrations (1 roentgenogram).

Aortic Aneurysms Simulating Organic Disease of the Gastro-Intestinal Tract. Samuel Baer and Samuel A. Loewenberg. Gastroenterology **10**: 617–625, April 1948.

Aortic aneurysm may assume many guises and frequently fails to present classical symptoms. Often the only complaints and dominant symptoms are referred to the gastro-intestinal tract.

Following a brief review of the anatomy of the aorta, including its relations to the esophagus and other parts of the digestive tract, the author presents 8 cases in which various gastro-intestinal lesions were suspected. The true etiology was found at necropsy in 7 of these patients; in the eighth it was determined by x-ray studies. Aortic aneurysm was confused with cirrhosis of the liver with esophageal varices, carcinoma of the esophagus, chronic cholecystitis, peptic ulcer, gastric carcinoma, and mesenteric thrombosis. The most unusual of all was a case of abdominal aneurysm which had separated the right lung from the diaphragm and depressed the right lobe of the liver. Spicules of calcium in the wall of the aneurysm led to a diagnosis of echinococcic cyst of the liver.

An awareness of the possibility of aneurysm in cases of weight loss, difficulty in swallowing, hematemesis, melena, or abdominal pain, will make it much easier to arrive at a correct diagnosis. Displacement of the barium-filled esophagus to the left and anteriorly is an almost pathognomonic sign.

One roentgenogram; 1 drawing.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

THE DIGESTIVE SYSTEM

Esophageal Hiatal Hernias of the Short Esophagus Type: Etiologic and Therapeutic Considerations. Arthur M. Olsen and Stuart W. Harrington. J. Thoracic Surg. **17**: 189–207, April 1948.

There are three types of esophageal hiatus hernia. In the first type, the "para-esophageal hiatal hernia", the esophagus is of normal length and its lower end is not elevated above the diaphragm. In the second type the esophagus is also of normal length, but the lower end has moved up with the stomach and is found above the diaphragm. This is called the "sliding or gastro-esophageal type" and is by far the most common. The third type is the short esophagus with partial thoracic stomach. This group comprised 10 per cent of all the hiatal hernias seen at the Mayo Clinic during the eleven-year period studied and numbered 220 cases.

The diagnoses were made by roentgenographic examination, esophagoscopy, and in some cases biopsies. Differentiation between the short esophagus type of hernia and stricture of the esophagus was occasionally difficult, and in such cases biopsies showing gastric mucosa just below the stricture were necessary to establish the diagnosis.

Symptoms may be numerous and diverse or there may be none. Epigastric or substernal distress, worse after meals and intensified by lying down, suggests a hiatal hernia. The syndrome may simulate ulcer, gallbladder disease, functional disorders, obstruction, or coronary disease. Dysphagia is the most common complaint, especially in the short esophagus type of hernia. It was present in 75 per cent of this series and in 76 cases it was intermittent, indicating the role of spasm. Eighteen patients had gross hemorrhage.

The congenital short esophagus comprised only 4 per cent of the 220 cases. All of this group had strictures and were successfully treated by dilatations; in all the hernia was thought to date from birth.

The authors feel that the basic abnormality in all cases of hiatal hernia is enlargement of the hiatus due to a delay in the descent of the stomach in the embryo. Eventually the stomach continues its descent and the hiatus remains too large. Later in life, for various reasons such as vomiting, peptic ulcer, etc., esophagitis develops and results in scarring and shortening of the esophagus and pulling up of the stomach. The diaphragmatico-esophageal membrane is not strong enough to hold the organ down. In some way or another, 96 per cent of the cases fall into this group. In 9 cases the patients had scleroderma, which is supposed to involve the wall of the esophagus and to be responsible for the shortening. Two cases were associated with long standing cardiospasm. Four patients had associated carcinomas, three of which were gastric in origin.

Another theory is advanced that reflex spasm of the esophagus due to vagal stimulation may cause some cases of retraction of the esophagus and eventuate in scarring and permanent shortening.

Treatment consists largely in dilatation of the strictures. Only 17 cases were operated upon in an attempt to reduce the hernia. In 4 cases a phrenic paralysis was produced and 3 of the patients benefited from this procedure. Medical treatment is directed against esophagitis.

Seventeen roentgenograms; 1 drawing; 1 chart; 6 tables.

HAROLD O. PETERSON, M.D.
University of Minnesota

Carcinoma in a Thoracic Stomach (Congenital Short Œsophagus). Robert Mailer. Brit. J. Surg. **35**: 426–428, April 1948.

Few cases of carcinoma in a thoracic stomach have been reported. The present case is recorded, however, not so much for its rarity, but rather for its illustration of the diagnostic pitfalls which may be met.

The patient was a woman of 49 complaining of attacks of pain in the lower left chest. An x-ray study revealed a hiatus hernia and, without resort to esophagoscopy, operative repair was undertaken. Symptoms recurred two weeks postoperatively and a roentgen study at that time revealed a short esophagus with a filling defect in the thoracic stomach. This was verified endoscopically, and a biopsy diagnosis of "poorly differentiated adenocarcinoma" was made. The cancer-bearing portion of the stomach was removed and the stomach anastomosed to the esophagus in a second operation, details of which are discussed. Of added interest is the comment that "cicatricial contraction of the new-growth pulling still more of the cardia above the diaphragm" was responsible for hiatus hernia in this patient. A similar mechanism in carcinoma of the esophagus produces *acquired* short esophagus.

Three roentgenograms.

JAMES ALLAN READ, M.D.
The Henry Ford Hospital

Experimental Studies on the Motility of the Gastric Mucosa in Dogs. A Preliminary Report. Frank P. Brooks, Lloyd W. Stevens, Eugene P. Pendergrass, and Francisco Bassols. Am. J. Roentgenol. **59:** 482–491, April 1948.

The literature on roentgenographic studies of the movements of the stomach is reviewed. Since none of these studies appeared to be entirely satisfactory, the authors devised their own technic. First, laparotomy was performed, thorotrast was injected into the submucosa of the stomach in four different areas, and lead shot was sutured under the serosa along the greater and lesser curvatures. Subsequent roentgenograms over a period of several months showed the thorotrast spread evenly through the submucosa of the entire stomach.

For the roentgen study the stomach was filled with water and air or a very dilute barium suspension and films were exposed, with and without various smooth muscle stimulating drugs. The reproductions show conclusively that the relief pattern of the mucosal folds does change independently of the muscularis propria. Changes were seen also with contractions of the muscularis propria. Thus the muscularis mucosae is capable of producing changes in the mucosal pattern.

Sixteen roentgenograms; 6 photomicrographs.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Peptic Ulcer and Functional Dyspepsia in the Armed Forces. Maurice H. Friedman. Gastroenterology **10:** 586–606, April 1948.

Careful observations were made on 138 patients with gastro-intestinal complaints admitted to an Army Air Force Station Hospital, in whom a diagnosis of active peptic ulcer or functional dyspepsia was made. To reduce the personal factor to a minimum, the histories were taken by the author in every instance and the roentgenologic studies were all made by the same roentgenologist.

In the 46 patients with a diagnosis of ulcer, regular postprandial pain relieved by food (particularly milk) was the most common and reliable symptom. Certain foods or beverages definitely exaggerated the discomfort, the chief offenders being alcohol, coca cola, coffee, and highly seasoned foods. The Palmer provocative acid test was positive in all cases in which the pain pattern permitted its use. Nausea and vomiting occurred in only 2 cases. The diagnosis of ulcer was corroborated by the x-ray studies in 31 of the 46 cases. It is noteworthy, however, that among the 15 unconfirmed cases, 7 showed massive hemorrhage and there was one perforation.

In the group of 92 cases classified as functional dyspepsia, there was regular postprandial pain in 60, but the interval between food and pain was short, characteristically from five to thirty minutes. The epigastric distress was variable, described as burning, a sense of pressure, ache, or fluttering. Nausea and vomiting were common presenting complaints. Intolerance to greasy foods was a frequent observation. There was otherwise no reliable evidence of particular dyspepsia. The Palmer acid test was negative in all cases in which it was used, and is considered of first importance in the differentiation of peptic ulcer and functional dyspepsia. X-ray studies were carried out in 70 cases in this group. In all but 4 they were entirely negative except for occasional evidence of duodenal irritability.

Following a lengthy discussion, in which 13,000 cases of dyspepsia from the war literature are reviewed, the author stresses the need for an objective analysis of the relation of psychological factors to the genesis and development of peptic ulcer. He feels that a satisfactory solution to the ulcer problem requires the cooperative efforts of many men working as a group enterprise.

Other conclusions are: (1) that there is no definite evidence that the emotional background of the ulcer patients was any different from that of other soldiers; (2) that there is no clear cut evidence that the strain of military service, including combat, was associated with any increase in the frequency of peptic ulcer; (3) that too much reliance is placed on x-ray examination for the diagnosis of peptic ulcer in the Armed Forces; (4) that we do not possess an adequate body of data on the frequency of ulcer in the civilian population or the limits of error in its x-ray diagnosis.

Two tables.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

Roentgenographic Studies of the Gastrointestinal Tract Following Section of the Vagus Nerves for Peptic Ulcer. Max Ritvo and Irving A. Shauffer. New New England J. Med. **238:** 496–501, April 8, 1948.

A study is reported of 33 patients who underwent vagus nerve resections for intractable peptic ulcer. The series included 30 men and 3 women, with ages ranging between twenty-one and fifty-seven years. Twenty-one patients had not been treated surgically prior to nerve resection. Postoperatively all of this group showed gastric dilatation and atony of the stomach. In all there was retained secretion and in 14 patients there was marked delay in both the initial and final gastric emptying. Three patients had complete retention at six hours.

Three patients had had previous gastro-enterostomies. In these there was slight dilatation of the stomach after vagotomy. Two of the number had slight retention after six hours and one had 100 per cent retention at six hours but at a subsequent examination, six months later, the stomach emptied completely in three hours.

Five patients had had partial gastrectomies. Following vagotomy all these patients showed gastric dilatation, with retained secretions, and 10 to 15 per cent gastric residue in six hours.

Vagotomy was followed by disappearance of the ulcer craters. Shortly afterwards, there was no tenderness, but there was some delay in gastric emptying in all instances. The small bowel showed no marked change except slow motility.

Seven roentgenograms.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Prolapse of the Gastric Mucosa Through the Pyloric Canal into the Duodenum. Report of 16 Cases Diagnosed Roentgenologically. Isaac Hall Manning, Jr., and George P. Highsmith. Gastroenterology **10:** 643–659, April 1948.

In spite of the small number of proved cases reported, it is the opinion of the authors that prolapse of the gastric mucosa is more common than is generally

recognized. They encountered 16 cases in a three-year period in which roentgen and clinical findings were consistent with this diagnosis.

The etiology of the condition is uncertain, but it may be due to failure of the normal cephalad movement of the gastric mucous membrane during antral systole. Antral gastritis, with inflammatory infiltration of the muscularis mucosae, may be either a contributory or underlying cause.

There is no characteristic symptom complex, and the diagnosis is usually made from roentgenographic studies. The variable upper gastro-intestinal symptoms are epigastric discomfort, burning pain, belching, bloating, regurgitation, nausea, and vomiting.

In all of the cases reported, the most reliable finding has been a constant "umbrella" or "mushroom" deformity in the base of the duodenal cap, with or without elongation and narrowing of the pyloric channel and increase in the size of the rugae of the pylorus and antrum.

In none of the 16 cases reported was operation considered necessary, but the authors believe that the diagnosis should not be deferred until surgical confirmation can be obtained. They feel that surgical therapy should be reserved for those cases with pyloric obstruction, polyp formation, hemorrhage, or suspected malignant change.

Eighteen roentgenograms.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

Pyloric Obstruction Due to Gastric Diverticulum. Report of a Case. J. G. Probstein, and Leo A. Sachar. J. Missouri M. A. **45:** 276–277, April 1948.

An instance of a diverticulum extending into the wall of the stomach and producing a rather severe grade of pyloric obstruction in a 62-year-old woman is described. This diverticulum did not protrude from the stomach, but rather grew into its wall; the opening was in the duodenum, and the lining mucosa was like that of the stomach. Serial compression spot roentgenograms demonstrate the filled diverticulum in the antral wall on the greater curvature side. Its shape is shown to change during antral systole and its encroachment upon the prepyloric antrum is also seen. Uneventful recovery followed partial gastric resection.

Four roentgenograms; 1 photomicrograph; 1 drawing.

ALTON S. HANSEN, M.D.
Peoria, Ill.

Non-Vitaminic Factors Involved in the Production of the "Small Intestinal Deficiency Pattern." W. H. Glass. Gastroenterology **10:** 660–666, April 1948.

Glass reports 5 cases with prepyloric, pyloric, or postpyloric lesions apparently causing a disordered motor function pattern of the small intestine without specific small intestinal disease. He points out that, if an upper small intestinal pattern is considered abnormal, one must attempt to delineate exact radiographic criteria of abnormality; thus, if areas of segmentation, hypertonicity or hypotonicity occur, they must be compared in dimension to contiguous areas. The point is also made that, unless the outlet from the stomach, pylorus, or surgical stoma is well functioning so that the bolus is of adequate size, the barium will not be dispersed over a sufficiently large segment of the small bowel for adequate visualization and evaluation.

The cases may be summarized as follows: Case 1 represented duodenal spasm with disordered motor function which responded to antispasmodics and psychotherapy, but not to Vitamin B complex. Case 2 was an organic prepyloric obstruction due to fibrocarcinoma, with a grossly abnormal jejunal pattern. Subsequent to gastrectomy, the stoma functioned well and the jejunal pattern returned to normal. In Case 3 a Ménière's syndrome was associated with duodenal ulcer and pylorospasm. The jejunal pattern was found to be abnormal precisely at the time of a Ménière's attack. Case 4 was that of a patient with a gastrojejunal ulcer with abnormal function of the stomach and marked jejunal segmentation. There was no response to Vitamin B complex parenterally. Subtotal gastrectomy with a well functioning stoma resulted in a return of the small intestinal pattern to normal. Case 5 was one of watery diarrhea and vomiting occurring only on Sunday. The patient, a man of thirty-four lived with and supported his psychotic mother, whom he personally took care of only on Sunday. The small intestinal pattern was grossly abnormal with marked scattering and areas of hypotonicity and hypertonicity. The duodenal cap was spastic, as was the distal colon. Large amounts of Vitamin B complex together with antispasmodics were not particularly effective. Psychotherapy is the treatment of choice in such a case.

The author concludes that an abnormal small intestinal mucosal pattern can be caused by multiple factors other than a deficiency of Vitamin B complex.

Five roentgenograms.

EDWARD E. LEVINE, M.D.
Dearborn, Mich.

Primary Tumors of the Small Intestine. Carroll C. Dundon. Am. J. Roentgenol. **59:** 492–504, April 1948.

The records of 62 primary small bowel tumors seen over a thirteen-year period at the University Hospitals of Cleveland are analyzed with reference to symptoms and x-ray findings. The series included 18 malignant tumors, in 13 of which there were symptoms referable to the gastro-intestinal tract or a palpable abdominal mass. Of the 44 benign tumors, only 2 caused symptoms, due in each instance to intussusception; 42 were incidental operative or autopsy findings.

In only 11 of the 18 patients with malignant tumors was a roentgen examination made, and only 8 had barium studies. The findings in the 8 cases were as follows: irregular narrowing in 4 cases, complete obstruction in 2 cases, dilatation of the bowel and hypermotility in 1 case each. Abdominal pain, vomiting, diarrhea, and weakness were the chief complaints in the malignant cases. Two patients had melena; no mention is made of examination of the stools for occult blood in the other cases. Nine patients had palpable tumors. The importance of earlier diagnosis is again emphasized by the fact that most of the patients had metastases by the time the disease was diagnosed. There was but one three-year survival and one patient was alive at the time of the report, having survived twenty months.

Twelve carcinomas were found, 3 in the duodenum, 5 in the jejunum, and 4 in the ileum. Two lymphosarcomas and 1 leiomyosarcoma were found in the jejunum. One fibrosarcoma and 2 malignant carcinoids occurred in the ileum.

One of the objects of this study was to see whether a group of patients could be selected on the basis of symptoms in which the possibility of tumor was great enough to justify special examination of the small intestine, a time-consuming and expensive procedure. It is concluded that "patients who have persistent abdominal pain, either intermittent or constant, and patients with vomiting, melena, or diarrhea which remains undiagnosed after routine studies of the gastro-intestinal tract, gallbladder, and urinary tract deserve special study of the small intestine to exclude a primary tumor.

"Carcinoma of the small intestine characteristically causes an irregular constriction of the bowel, 2 to 6 cm. in length, with a tortuous column of barium through the lesion. Lymphosarcomas can occasionally be identified because the lumen of the tumor is larger than the normal intestine. Many of the primary tumors have no special roentgenographic picture, and the duty of the radiologist is to locate the lesion as 'obstruction of unknown cause.' "

Eight roentgenograms; 3 photographs; 3 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Unusual Anomaly of the Gallbladder and Bile Duct. B. L. Sinner. J. Missouri State M. J. **45:** 265–266, April 1948.

An anatomical anomaly is described in which the cystic duct began at the fundus of the gallbladder, ran under the mucosa to the gallbladder neck, and then continued downward behind the duodenum well into the pancreas, where it united with the hepatic duct. Shortly beyond the point of junction the pancreatic duct joined the common duct. The gallbladder neck was a blind pouch.

The patient was a man of 60 years, operated upon for acute pancreatitis superimposed on common duct stone. The operative findings and cholangiographic observations are presented.

One roentgenogram; 1 drawing.

ALTON S. HANSEN, M.D.
Peoria, Ill.

Gallbladder Gas Gangrene. Roswell K. Brown and Elmer Milch. Gastroenterology **10:** 626–633, April 1948.

Infection of the biliary tract with the organisms of gas gangrene has been reported occasionally during the past fifty years. While it has not been recognized as a frequent occurrence, the authors do not consider it rare. They state, however, that one should be cautious in attributing disease to *C. welchii*, since the organism is not uncommonly found in wounds of healthy persons; it may also be present in normal liver and multiplies rapidly after death. Clinically, emphysematous cholecystitis is similar to other types of acute gallbladder disease.

Of 39 patients dying after biliary tract surgery at the Buffalo General Hospital, 6 apparently had *C. welchii* infection. In 2 cases infection had spread from the gallbladder bed to the liver; 2 patients had massive involvement of the abdominal wall and abdominal abscesses occurred in the other 2. Hematemesis was observed in 2 of these fatal cases and "brown" vomitus in two others. A seventh patient, who survived, had "black" stools.

The diagnosis of acute gaseous cholecystitis may be made by roentgenography, which reveals a gas shadow in the gallbladder region. Reproductions of radiographs in a patient who survived show a gas shadow in the right upper quadrant with clear evidence of dissection of gas about the gallbladder wall. Large doses of penicillin and sulfadiazine were administered to this patient. Gas in the gallbladder was still present on the 24th day of the disease, but was absent on the 35th day.

The authors conclude that hematemesis may be considered a possible presumptive sign of gallbladder gas gangrene and they believe penicillin should be used routinely as a prophylactic measure in all biliary tract surgery.

Three roentgenograms; 1 photomicrograph.

EDWARD E. LEVINE, M.D.
Pontiac, Mich.

Acute Pneumocholecystitis. Carl J. Heifetz and H. R. Senturia. Surg., Gynec. & Obst. **86:** 424–433, April 1948.

By acute pneumocholecystitis is meant an acute infection of the gallbladder characterized by the production of gas within the lumen. As the term is used here, it does not include gas from fistulas between the gastro-intestinal tract and the gallbladder, gas in the gallbladder in cases of generalized *perfringens* infection, or gas in the gallbladder as a postmortem change. The diagnosis can be made radiographically, the gallbladder being visualized through the contrast medium of gas.

The authors reviewed the literature of the last forty-five years and uncovered only 8 bona fide cases of acute pneumocholecystitis. In this paper they add two more proved examples.

The surgeon should be interested in the demonstration of this entity, for certain peculiar features of the disease pose problems in surgical management. While a majority of normal and diseased gallbladders are sterile, others contain a wide variety of bacterial flora, headed in frequency by *Escherichia coli communis* and *Clostridium perfringens*. Besides these, other gas-forming organisms, often difficult to classify, may exist in the bile tract. In cases showing acute cholecystitis and gas in the gallbladder, early surgery is indicated because of the tendency of the gallbladder wall to become necrotic and of gas to escape into the pericholecystic tissues. Polyvalent gas antiserum, sulfonamides, and roentgen therapy, according to the authors, are of questionable value in the management of this condition.

Due to the great risk of gangrene of the gallbladder and consequent perforation, it is advisable to search for this type of case by obtaining routine scout or survey films of the gallbladder area in all instances of clinical cholecystic disease.

Six roentgenograms; 2 charts; 1 table.

MARLYN W. MILLER, M.D.
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Congenital Cystic Dilatation of the Common Bile Duct: Report of a Case. John L. Keeley. Arch. Surg. **56:** 508–515, April 1948.

This report concerns a 30-year-old man on whom operation was performed for chronic gallbladder disease. Preliminary x-ray study had failed to visualize the gallbladder and had revealed changes in the gastro-

intestinal tract interpreted as duodenal ulcer with partial pyloric obstruction. The operative findings were a congenital cystic dilatation of the common duct containing bile and stones, compressing the first portion of the duodenum. The structure of this cyst was such as to leave a valve-like fold at the exit when the cyst was not distended, causing an intermittent obstruction. A "Roux en Y" anastomosis was made; *i.e.*, the jejunum was divided and the distal end anastomosed to the cyst, while the proximal end was anastomosed laterally to the jejunum 12 inches distally. The gallbladder was then drained. Subsequent study with contrast medium showed the gallbladder, the cyst filled with air, and the jejunal loops. The patient recovered, with complete relief of symptoms and no evidence of ascending cholangitis. The lesion is a rare one, thought to be caused by a combination of congenital and dynamic factors. The triad of abdominal pain, abdominal mass, and jaundice are said to be "almost diagnostic." Although a correct preoperative diagnosis is highly desirable, prompt recognition of the lesion when it is exposed at operation is imperative, so that appropriate measures may be taken without delay

Two roentgenograms; 1 photograph; 3 drawings.

LEWIS G. JACOBS, M.D.
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A Case of Congenital Choledochus Cyst. S. Urwitz. Acta paediat. **35:** 168–172, 1948.

A case of choledochus cyst in a young boy is reported. The first evidence of the condition was the discovery of an abdominal mass after the child started to school. This was demonstrable roentgenologically but appeared on successive examinations to vary in size. Symptoms were at first minimal, but subsequently severe jaundice developed. Injection of abrodil showed a cyst measuring 9 × 16 × 14 cm.; extending from this, like an appendage, was the normal-sized gallbladder. The patient died postoperatively of a biliary peritonitis, but the author believes that the diagnostic procedure here described, if done at an earlier stage, should make possible operation in time to save the patient.

One roentgenogram.

Pancreatic Lithiasis and Renal Lithiasis in the Same Patient. George M. Fister and Anthony J. Lund. Urol. & Cutan. Rev. **52:** 214–217, April 1948.

The authors found the association of bilateral renal calculi and pancreatic lithiasis twice recorded in the literature. They report a third case. A diagnosis of bilateral urinary lithiasis was made in 1936. The patient had a complete urological investigation with pyelograms of the upper urinary tract again in 1941, 1943, and 1947. Only in the last year was evidence found of pancreatic lithiasis. A plain abdominal film at that time showed multiple calcifications distributed obliquely across the upper abdomen, outlining the location of the pancreas. It is believed that these represent calcifications in the pancreas itself and the lateral film adds additional evidence for this assumption. Opacities were also noted in the region of the mid-ureter, inferior major calyx on the right side, and mid portion of the left kidney. Retrograde urography confirmed the location of the urinary concretions.

Four roentgenograms; 2 tables.

THE MUSCULOSKELETAL SYSTEM

Chondromyxoid Fibroma of Bone. A Distinctive Benign Tumor Likely to be Mistaken Especially for Chondrosarcoma. Henry L. Jaffe and Louis Lichtenstein. Arch. Path. **45:** 541–551, April 1948.

The authors have encountered 8 examples of a rather distinctive benign tumor of bone whose anatomic peculiarities seem best expressed by the name "chondromyxoid fibroma." So far the lesion has been found only in the lower extremities.

Consistently, the patients complained of some pain, which was intermittent and not very distressing. Most of them had been aware, for some time, of the presence of a palpable mass at the affected site.

Though simulating cartilage tumor tissue grossly, the tissue of chondromyxoid fibroma lacks the blue-white luster and the faceted pattern of the former. In the main it is whitish, rather glistening, and firm but compressible. Also, despite the myxoid character of the intercellular matrix, grossly the tissue does not appear slimy.

The tumor destroys the bone at the site of its growth, and residua of the original spongy trabeculae are not usually found within it. Where it abuts on the cortex, it tends to erode and destroy this. As the original cortex gives way, the contour of the affected area of the bone becomes bulged. The expanded contour may be outlined, in part or throughout, by a thin shell of bone newly deposited by the periosteum. However, where a demarcating cortical shell is absent, gross examination will reveal that the tumor is still contained by the periosteum and the overlying parosteal connective tissue. That is, the tumor tissue does not violate the bounds of the periosteum. Furthermore, as noted, the tumor usually does not extend across the entire width of the bone at the site of its growth. Along its inner surface, one usually finds it bordered by a smaller or larger zone of sclerosed and often distinctly grooved osseous tissue.

These various gross features of the lesion find their reflection in its roentgen picture. First, the tumor is usually of appreciable size. Also, though located by predilection in a metaphyseal area of a tubular bone, it ordinarily does not encroach on the epiphyseal end proper. While the disease focus may appear roundish, it is usually ovoid in shape. Its long axis is usually in the long axis of the affected bone. In one or another instance it has measured as much as 7 or 8 cm. in its longest dimension and 4 or 5 cm. across.

In conformity with the absence of osseous trabeculae in the tumor tissue, the area of the lesion appears, on the whole, radiolucent. Since its advance in the interior of the bone is associated with the development of a sclerosed perifocal osseous margin, which may be distinctly grooved, the area of the lesion may also present coarse trabeculation roentgenographically. The external border may be demarcated roentgenographically throughout by a more or less expanded thin shell of bone, or it may be difficult to visualize in places because no periosteal cortical shell has been laid down there.

On the whole, the roentgen picture has a certain distinctiveness, at least when the lesion is in a long bone and has attained appreciable size. However, even when it is in a long bone, and certainly when in other sites, clinical recognition on the basis of the roentgen appearance may be difficult. In particular, one may

have to consider, in relation to differential diagnosis, the possibility of a focus of fibrous dysplasia, a rather atypical unicameral bone cyst, or even enchondroma. The likelihood of confusing chondromyxoid fibroma with giant-cell tumor roentgenologically is remote.

Microscopically, the tissue of a particular specimen may simulate cartilage tissue in one area or another, thus justifying the qualification "chondroid." However, in some specimens one may fail to find such areas at all, and in any case the tumor tissue fundamental to the lesion is clearcut in its deviation from hyaline tumor cartilage tissue. Indeed, the basic cytologic picture of the lesion is that of a peculiarly differentiated connective-tissue tumor whose cells lie loosely in a myxoid intercellular matrix which, in one or another tumor or tumor area, may undergo substantial collagenization. The presence, in the tumor tissue, of smaller or larger numbers of cells exhibiting nuclear atypism may give the cytologic picture of the lesion a false cast of ominousness, explaining why it may come to be misinterpreted as a cancer.

Chondromyxoid fibroma is a benign lesion and does not tend to recur even after mere curettage. Thorough curettage of a large lesion may make filling of the bone defect with bone chips or a bone graft desirable. Six of the authors' cases have been followed from one and one-half to seven years, and in none has there been a local recurrence. One of the 2 remaining cases is recent, and the other has been lost to follow-up.

Six roentgenograms, 6 photomicrographs.

Occult Bone Metastases. Ralph Shackman and C. V. Harrison. Brit. J. Surg. **35:** 385–389, April 1948.

In a generously illustrated paper, the authors discuss the discrepancy between recent x-ray reports and the anatomical findings in bone metastases. Color photographs of gross postmortem specimens show extensive lesions which were "radiologically invisible" even on direct contact radiographs. Although the failure of clinical radiographs rests in part with obscuring soft-tissue density, the authors suggest that the x-ray method fails largely because tumor must fully replace the involved marrow spaces before bone reaction is excited and density changes can occur. They conclude that so-called normal radiographs cannot exclude even extensive bony metastases.

Twelve roentgenograms; 10 color photographs; 4 photomicrographs. JAMES ALLAN READ, M.D.
The Henry Ford Hospital

The Serious Limitations and Erroneous Indications in the Diagnosis of Tumours of Bone. James F. Brailsford. Proc. Roy Soc. Med. **41:** 225–236, April 1948.

Since a synopsis of this article has appeared as an editorial in RADIOLOGY, it need not be abstracted here. The reader is referred to the editorial, in the November 1948 issue, and to the discussion to which it gave rise, on pages 432-434 of this issue.

Gargoylism (Lipochondrodystrophy). A Review of Clinical Observations in Eighteen Cases. William Anthony Reilly and Stuart Lindsay. Am. J. Dis. Child. **75:** 595–607, April 1948.

Gargoylism is a disease involving most of the tissues of the body. The skeleton is greatly altered and may be the earliest site of clinical manifestations. All of the 18 patients in the authors' series had fairly pronounced skeletal changes, including short stature, short thick neck, kyphosis, and inability to extend the joints fully. They stood in a crouched attitude, with the thighs partially flexed and abducted, the knees in genu valgum, and the feet everted. In many patients the long bones were thickened and deformed at their ends, and the hands were occasionally in a position of ulnar deviation, owing to the obliquity of the lower radial epiphysis. The small joints of the wide, stubby hands and feet were partially flexed, giving the fingers and toes a claw-like appearance. Other clinical features include the characteristic facial appearance which has given the disease its name, hepatosplenomegaly, cloudy corneas, umbilical hernia, and mental retardation.

Roentgenologically the configuration of the skull is seen to be abnormal. It is usually considerably longer in its anteroposterior dimension than in its width, which is greatest in the temporal region. The frontal areas overlie the orbits anteriorly to a considerable degree. The sella turcica is greatly elongated anteroposteriorly and is shallow. The clinoid processes often are poorly developed and stand upright. They are not eroded. Often there are numerous convolutional markings on the inner table of the skull. The maxilla, and in many patients the ascending mandibular rami, are underdeveloped. The mandibular angles are greatly increased.

The scapulae are frequently widened. The ribs have narrow roots and broad bodies, with necks which appear distorted. Often they leave the spinal column at almost a right angle. The clavicles are distorted and wide. The superior halves of some of the vertebral bodies (between the twelfth thoracic and second lumbar level) do not ossify at the same rate as the inferior halves, so that a step-like formation on their anterior surfaces is produced, resulting in the kyphosis so often noted clinically.

Changes are more pronounced in the upper than in the lower extremities. Characteristically, there are decided retardation of epiphyseal maturation, abnormal configuration of the shafts and irregular cartilaginous proliferation at the epiphyses. The shafts are short and stubby and exhibit bizarre swellings in the central portions, which taper toward the ends, this latter feature being a significant diagnostic sign. The head of the humerus is thick and exhibits a valgus angulation. The articular surfaces and the epiphyseal plates of the lower ends of the radius and ulna (or occasionally of only one of these bones) face inward. The metacarpal bones and proximal portions of the metatarsals and the phalanges are broad and shortened, and the first two phalangeal bones are pointed at their ends. Both acetabula are shallow and the ischia are disproportionately small in relation to the ilia. The femurs show a coxa valga angulation at the neck and a malformed, flat appearance of the head. The necks are broad. Invariably genu valgum is present, owing to the tilted epiphyses and lines of the femurs and tibiae. The feet show the same characteristics as the hands. The epiphyseal plates of the long bones are usually flat and deformed and often have irregular outlines of ossification. Occasionally there is a fragmentation in the ossification process. Retarded epiphyseal age was observed in about half the patients. Invariably kyphosis was found roentgenographically, and in an

infant this should be regarded as strongly suggestive of gargoylism, especially if tuberculosis and other common causes of the condition can be ruled out.

Of this series of cases, 8 came to autopsy. The pathological features are reserved for a later paper.

Three roentgenograms; 1 photograph.

Osgood-Schlatter's Disease. William W. Kridelbaugh and Alvin C. Wyman. Am. J. Surg. **75:** 553–561, April 1948.

The authors found 13 cases of so-called Osgood-Schlatter's disease among 9,250 inductees at a Naval Recruit Training Center, all but 2 in youths 17 years of age. The most common complaint was pain over the tibial tubercle. In far advanced cases this is almost constant, but early in the course there may be pain only when a pulling force is transmitted to the tibial tubercle by the patellar tendon. Sixty-nine per cent of the patients gave a history of trauma preceding the pain. There were always a moderate to marked soft-tissue swelling and bony irregularity over the area of the tibial tubercle. Tissue tenderness to pressure was also a constant finding.

Ossification of the proximal tibial epiphysis appears just before or after birth. Downward ossification of this epiphysis occurs or a secondary center of ossification appears in the tubercle at approximately eleven years. Fusion of the tubercle usually occurs by nineteen years.

The authors conclude that the entity known as Osgood-Schlatter's disease may be one of three distinct processes:

(1) Simple epiphyseal separation. Fragmentation and necrosis may follow.

(2) Aseptic necrosis of the tibial tubercle with or without epiphyseal separation. The primary process is an avulsion fracture of the tubercle. Ten of the 13 cases reported were of this type.

(3) Fragmentation and necrosis of the epiphysis, with or without epiphyseal separation. This corresponds to the usual description of Osgood-Schlatter's disease. It was the type seen least often in the authors' cases.

Epiphyseal separation and fragmentation may be acute and the result of recent injury or may be an old process with or without symptoms. The roentgen criteria for activity depend on the appearance of the adjacent margins of the separated epiphysis, changes in bone density, alteration in the size and architecture of the fragments, thickening of the adjacent soft tissue. Extraneous calcifications in the tubercle are, for the most part, avulsed particles.

Osgood-Schlatter's disease must be differentiated from a pyogenic infection and from syphilitic and tuberculous osteomyelitis. These all involve medullary and cortical bone primarily and the epiphysis secondarily.

Treatment in the cases reported here was conservative, consisting in cross-strapping with adhesive tape. Six patients showed improvement and 2 no improvement; 2 were made worse and 3 were not followed.

Four roentgenograms; 5 drawings; 2 tables.

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University of Pennsylvania

Infantile Cortical Hyperostoses. W. van Zeben Acta paediat. **35:** 10–20, 1948.

Three cases of infantile cortical hyperostoses are reported. The only clinical symptom was swelling of the lower legs. Roentgen examination showed thickening of the periosteum of the tibiae and along other bones, with no evidence of soft-tissue swelling. Features not heretofore described, observed in the author's cases, were occurrence within the same family and marked forward curvature of the tibiae.

Eleven roentgenograms; 1 photograph; 1 genealogical chart.

An Osseous Dystrophy with Many Pseudo-Fractures. J. F. Curr. Brit. J. Surg. **35:** 411–414, April 1948.

An account is given of a 25-year-old dwarf with a severe disabling osseous dystrophy characterized by generalized bone softening with slowly progressive weight-bearing deformities of spine, pelvis, and lower extremities, and multiple pseudo-fractures. The dwarfism, which "must have been associated with some generalized disorder of growth," was greatly exaggerated by the bowing of the lower limbs. An exhaustive clinical study of the patient was not possible. Roentgenograms were obtained, however, of the entire skeleton. These revealed little abnormality in the upper limbs, a wormian bone in the skull, several rib fractures, severe scoliosis of the spine, a trifoliate pelvis with pubic fracture, bowing of the femora with symmetrical diaphyseal fractures, and right-angle bowing of the legs with marked fibular hypertrophy. Notable in the leg bones were multiple Looser's zones, or small local infractions, situated atypically on the concave aspects; these did not change in appearance from 1943 to 1945. The blood phosphatase was elevated.

In the discussion of differential diagnosis, the author indicates that the picture conforms closely with no other disorder but has features in common with renal osteodystrophy, juvenile osteomalacia, and Milkman's syndrome.

Two photographs; 5 roentgenograms.

JAMES ALLAN READ, M.D.
The Henry Ford Hospital

Pseudarthrosis in the Lumbosacral Spine. Mather Cleveland, David M. Bosworth, and Frederick R. Thompson. J. Bone & Joint Surg. **30 A:** 302–311, April 1948.

With all the reports on lumbosacral fusion, very little information has been obtained as to the occurrence of pseudarthrosis after this operative procedure. This paper analyzes a large series of fusions with this point in mind.

Six hundred and forty-seven operative procedures were carried out on 594 patients and, of these, 20 per cent had pseudarthrosis. If the number of interspaces arthrodesed is counted, there were 1,329 spinal intervals bridged, with pseudarthrosis developing in 161 intervals, or a percentage of 12.1. If only the fifth lumbar interspace was bridged, the incidence of pseudarthrosis was 3.4 per cent; if the fourth and fifth lumbar intervals were bridged, the incidence was 17.4 per cent. As more intervals were included in the arthrodesis, the figure rose to 33.3 per cent.

In order to show adequately the failure of fusion, roentgenograms in the anteroposterior direction of the operative area were obtained: one in right lateral bending, the other in left lateral bending. A lateral view in flexion and another in extension were also made. When both anteroposterior views were superimposed, the extent of arthrodesis could be demonstrated by the

duplication of position of the involved vertebrae. The same procedure was followed with the lateral views of the region.

This article discusses the incidence of pseudarthrosis in herniation of the intervertebral disk, lumbosacral sprain, tuberculosis, spondylolisthesis, arthritis, and other conditions. Various operative procedures are discussed.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Secondary Echinococcosis of the Vertebral Column with Possible Medullary Spread. Diogo Furtado, Vasconcellos Marques, M. Azevedo Gomes, and Moradas Ferreira. Gaz. méd. Portuguesa **1**: 127–133, 1948. (In Portuguese.)

The authors describe a case of secondary echinococcosis with numerous vesicles localized in the tenth dorsal vertebra and corresponding left rib. The outstanding features of this case were pain and a paraplegia which was found on operation to be due to medullary pressure. Although all the hydatid vesicles producing pressure were removed, the condition of the patient showed no improvement. Subsequent myelography disclosed persistent obstruction of the spinal canal and further exploration revealed two small cavities within the medulla full of pus containing pneumococci. The patient remained paraplegic and died three months later.

Necropsy showed a total softening of the medulla at the site of the pressure, which made it impossible to establish the nature of the intramedullary lesion. The authors suggest the possibility of an intramedullary localization of hydatid vesicles with secondary infection.

Two roentgenograms; 1 drawing.

Cartilaginous Tumors of the Hand. John G. Shellito and Malcolm B. Dockerty. Surg., Gynec. & Obst. **86**: 465–472, April 1948.

Forty-two cases of cartilaginous tumors of the hand seen at the Mayo Clinic from 1908 to 1942 are reviewed. Only cases in which pathological study was possible are included. The operative specimens were sectioned; the case histories were reviewed; roentgenograms were examined, and the roentgen and pathological diagnoses were compared. There were 30 enchondromas (or "chondromas") and 12 ecchondromas (known also as "perichondroma," "osteochondroma," or "exostosis"). These tumors appear in the phalanges and metacarpal bones. Two of the enchondromas in the present series arose in a tendon sheath.

Enchondromas occur much more often in the hand than ecchondromas (3:1) but the relationship is reversed when the incidence of these tumors in all bones of the skeleton is considered. An enchondroma is usually a small cartilaginous tumor located centrally in the bone shaft, growing from many centers and expanding in all directions. These tumors may be single (25 of 30) or multiple (5 to 30) tumors. The roentgen appearance is that of the so-called bone cyst, a round area of decreased density in the center of the bone; the cortex is usually expanded and thin; fractures were found in 26.6 per cent of this series. These tumors, in comparison to normal hyaline cartilage, show increased vascularity, calcium deposition, and myxomatous degeneration.

The ecchondroma occurs peripherally in bone near the end of the shaft and has a bony base and cartilaginous cap. The roentgenogram shows an elevated bony structure in that location. No pathologic fractures were encountered.

The treatment in both types is conservative operation. Either tumor may recur, and this does not necessarily indicate malignancy. There was a single case of malignant change in this series, discovered at the fifth operation for a recurrent enchondroma.

Two roentgenograms; 3 photomicrographs; 2 photographs.

JORGE DE LA FLOR, M.D.
University of Pennsylvania

Lateral View of the Pelvis in Examination for Hip Dislocation. S. W. Donaldson, Carl E. Badgley, and W. G. Hunsberger. J. Bone & Joint Surg. **30 A**: 512–514, April 1948.

The authors suggest a lateral view of the pelvis, as in pelvimetry, to demonstrate injuries of the acetabulum or dislocation of the femoral head, though, if there are extensive fractures of the pelvis, this procedure obviously is not applicable. It is often more comfortable for the patient to lie upon the injured side, but adequate examination can be obtained if he lies on the uninjured side. This position will show any posterior or anterior displacement and will more clearly demonstrate the acetabulum injury than the usual stereoscopic views of the pelvis.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Results of Treatment of Congenital Dislocation of the Hip in Infancy. Frederic C. Bost, Helen Hagey, Edwin R. Schottstaedt, and Loren J. Larsen. J. Bone & Joint Surg. **30 A:** 454–468, April 1948.

This is a review of 86 patients with 112 dislocations of the hip for which treatment was begun within the first three years of life. The histories indicate that the signs and symptoms of hip dysplasia and dislocation were usually present early, and were often recognized by the parents and physicians before the diagnosis was established. These signs and symptoms were: a flexed and externally rotated hip, increased thigh folds, shortening of the thigh, clicking of the hip, prominence of the trochanter, limitation of abduction, and limp. Since early treatment is imperative in these cases, diagnosis must be made promptly. Often the diagnosis is not made and treatment is delayed until it is too late for satisfactory results.

Roentgenography is the basis upon which the anatomical condition of the hip is to be judged. The films must be made in the standard position with standard technic. The tube must be accurately centered and the pelvis flat, with the knees together and the patellas uppermost. Specific information concerning the acetabulum and the head and the neck of the femur, as well as their relationship, must be obtained. The Hilgenreiner measurements are adequate. In these measurements a line is drawn transversely through both acetabula at the tips of the ilia. Another line is drawn along the slope of the acetabulum of both ilia to intersect the base line. The angle between these two lines is computed for both acetabula and is known as the "acetabular index." A third line drawn perpendicular to the Y line to the highest point of the upper femoral diaphysis permits the measurement of the distance of the femoral diaphysis either upward or downward from

the Y line and also its distance outward from the tip of the ilium at the base of the acetabulum. Perkins' measurement, which is a perpendicular line from the upper and outer border of the acetabulum to the Y line, is also helpful in indicating the position of the head of the femur.

The Y co-ordinate of the hip joint is a measurement from the line of gravity of the body as represented by a longitudinal line drawn through the mid sacrum and measured to the center of the head of the femur. All these measurements and indexes are important, and accuracy depends upon proper and adequate radiography.

The earlier the treatment in the patient's life, the better the prognosis. The various measurements described are of great aid in determining progress and prognosis.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Congenital Pseudarthrosis. Follow-Up Study after Massive Bone-Grafting. Harold B. Boyd and Kermit W. Fox. J. Bone & Joint Surg. **30 A:** 274–283, April 1948.

Three types of patients with congenital pseudarthrosis are recognized: first, those born with the defect; second, those with fracture through a congenital cyst of the tibia; third, those with congenital bowing of the tibia with a small sclerotic bone and a narrow medullary cavity.

This paper deals with a follow-up report on 7 cases previously described in 1941 (Boyd: J. Bone & Joint Surg. **23:** 497, 1941). In 4 of these cases there was refracture of the tibia in which it was difficult to obtain union. Neurofibromata were not found, although *cafe-au-lait* spots were seen in several of these patients.

As refracture is prone to occur in these cases, adequate bracing following the bone graft should be maintained until the tibia is essentially normal in appearance. The tibia should be watched closely for many years to determine the earliest evidence of march fracture, recurring sclerosis, or narrowing of the medullary canal, which are early signs of refracture.

The 7 case reports are presented with adequate follow-up and the suggestion of dual bone graft as treatment.

JOHN B. MCANENY, M.D.
Johnstown, Penna.

Ectopic Bone Deposits. A Paraplegic Complication. Maurice B. Roche and Frederick A. Jostes. Am. J. Surg. **75:** 633–636, April 1948.

The authors discuss the occurrence of ectopic bone deposits in the soft tissues of paraplegics, and conclude that these are prone to occur as a consequence of continued recumbency and immobilization. In a study of 62 cases of paraplegia, quoted from an issue of the *U. S. Army Bulletin*, 23 showed ectopic deposits of trabeculated bone within the muscles or fascial planes, principally over the hip and knee joints. Ossification was recognized as early as forty days after cord injury. In analyzing this group of cases, it was found that patients showing degrees of recovery in function seemed to escape this complication. From various comparative clinical and laboratory studies made, no other factor appeared to play a role.

Mention is made of the fact that immobilization for prolonged periods depletes the store of calcium from the bones, resulting in hypercalcemia and hypercalcinuria, and consequent development of calculi in the urinary tract. Whether ectopic bone deposit is a reflection of the same process remains to be proved.

A case is reported, in which massive bridges of coarsely trabeculated bone were seen on roentgenographic examination to extend from the anterior portion of each ilium and the lower rim of each acetabulum to the anterior portions of the head, neck, and upper fourth of the femur. The structure of the hip joints and femora presented a normal appearance except for advanced atrophy.

In order to forestall the complication of ectopic bone deposits, mobilization as early as possible is undertaken. This is accomplished in the recumbent patient by the use of slings around the heels and knees attached to cords suspended over pulleys and arranged so that the patient is able to lift each extremity and thereby obtain complete flexion of ankle, knee and hip joints. Twice a day, in addition, the patient is placed prone on a cart with the feet over the end, permitting extension of hip and knee joints.

Two roentgenograms; 1 photograph.

DAVID S. MALEN, M.D.
University of Pennsylvania

GYNECOLOGY AND OBSTETRICS

Radiology as It Relates to Obstetrics. Robert D Moreton and T. F. Bunkley. Texas State M. J. **43:** 753–757, April 1948.

It is theoretically possible to demonstrate the fetal skeleton roentgenographically by the seventh week, but actually, according to the authors, this is seldom possible before the fourteenth week. For this reason, hormonal tests are usual in the diagnosis of early pregnancy, though occasionally roentgen evidence is demanded in court to differentiate between the pregnant uterus and a pelvic tumor or between pregnancy and pseudocyesis.

The information to be obtained concerning the fetus is discussed under five headings:

(1) Detection of multiple pregnancy.

(2) Verification of fetal death. Of the signs assembled by Schnitker, Hodges, and Whitacre (Am. J. Roentgenol. **28:** 349, 1932), the most reliable is overlapping of the fetal bones. The others are lordosis or angulation of the spinal column, collapse of the thoracic cage, lack of evidence of growth of the fetus on serial study, disproportion between the size of the fetus and the expected size, and decalcification of the fetal skeleton. [This last is an early sign and as the duration of fetal death increases and the bone actually becomes dead bone, it appears more dense, as in sequestra.—S.F.T.]

(3) Visualization of malpresentation.

(4) Determination of the age of the fetus, either by recognition of signs of maturity in the skeleton or by measurement of the roentgen image.

(5) Detection of fetal abnormalities, of which hydrocephalus is the most frequent.

Beside furnishing information regarding the fetus, obstetric radiology is useful for determination of the relationship of the fetus to the mother and to give information regarding the mother that may secondarily affect the fetus. Indications for roentgenologic pelvimetry are as follows:

(1) When the clinical examinations suggests an abnormality in the size or shape of the pelvis.

(2) When the obstetrician cannot make a satisfactory examination because of either precautions of asepsis when the patient has presented herself too late in pregnancy, or extreme obesity of the patient.

(3) In all cases where history reveals a previous dystocia, especially when accompanied by fetal death.

(4) In instances of previous trauma, fracture of the pelvis, or history of poliomyelitis or other deforming disease.

(5) During labor, to ascertain the site of arrest and aid in planning measures to overcome the dystocia.

(6) In elderly primiparas, especially when the breech presents or when extra precautions are being taken to insure the birth of a living baby.

(7) When the patient requests that such an examination be made.

The authors point out that the pelvis can be measured with an error no greater than 3 mm.

A final indication for roentgenologic study is to aid in the diagnosis of placenta praevia. In about 3 per cent of all pregnancies some type of vaginal bleeding occurs, and in about one-fifth of these, the bleeding is due to a placenta praevia. Although placentography is not infallible for the diagnosis, its accuracy is approximately 90 per cent and this is increased by re-examination with cystography. The location of the placenta may also be of importance when cesarean section is contemplated.

It is of interest that the authors believe "that roentgenographic examination should be carried out without definite knowledge of the obstetric findings; then, if there is agreement in the two opinions, our conclusions are more reliable." [This is an excellent example of the objectivity that radiology can give to the art of the practice of medicine, and it is this scientific aspect and this field in which the radiologist should be paramount—S.F.T.]

As a note of precaution, the authors point out that they do not believe that radiology gives the entire answer, but it should be accepted as a dependable aid, remembering that due recognition must be given to the fact that soft-tissue structures (the cervix in particular) and pelvic dynamics are also important factors.

Twelve roentgenograms.

S. F. THOMAS, M.D.
Palo Alto, Calif.

Roentgenologic Methods in Obstetrics. Martin Schneider. Texas State J. Med. **43:** 758–762, April 1948.

Schneider differs from Moreton and Bunkley (see preceding abstract) in placing the time at which the fetal skeleton becomes demonstrable on the roentgenogram at the seventeenth week. He covers many of the same points as to the value of radiology in obstetrics. The fetal age, he states, is subject to a close estimation by cephalic or extremity measurement and term may be anticipated with the definite identification of the proximal tibial epiphysis and/or the cuboid osseous nucleus. Death is apparent in the young fetus when it is seen collapsed low in the uterus or its position is unchanged after several days interval. For the older fetus, "Spalding's sign" in the absence of active labor with increased overlapping of the cranial bones and hyperflexion of the spine is quite reliable.

Ectopic pregnancy is usually diagnosed clinically, but occasionally hysterosalpingography may be of aid. One case is cited in which a roentgen diagnosis of abdominal pregnancy was made at term when engagement failed to occur.

Direct placentography can be done with soft-tissue studies of the pregnant abdomen. Amniography has not gained favor generally. Cystography as a supplement to the soft-tissue studies is frequently of considerable use. This author prefers air cystography rather than the use of a contrast medium.

Eleven roentgenograms.

S. F. THOMAS, M.D.
Palo Alto, Calif.

Roentgen Pelvimetry. E. G. Reuter. Texas State J. Med. **43:** 762–764, April 1948.

The author criticises Ball's method of pelvimetry on the ground that "it is like trying to look at a plate when it is turned obliquely, so that neither the surface from a perpendicular position nor the edge directly from the side can be seen." This is because the position described by Ball calls for the roentgen-ray tube to be directly over the pelvis so that the central ray shall pass perpendicularly to the film through the head of the fetus. The result is that the oblique diameters of the inlet cannot be measured in the anteroposterior projection, nor can the anteroposterior diameter or obstetrical conjugate.

The demonstration of the anteroposterior and oblique diameters of the inlet and its nature is possible only in the anteroposterior projection, either by the method of Thoms, in which the plane of the pelvic inlet is parallel to the film with the patient seated, or a method previously published by the author, in collaboration with Reeves (Am. J. Roentgenol. **42:** 847, 1939), in which the patient is recumbent and the rays pass obliquely through the inlet toward the feet at an angle of 12.5 degrees from the vertical, just inferior to the anterior superior spine of the ilium. A simplification of the original scale for the measurement of roentgenograms made by this latter technic is given.

A case is reported, which the author believes explains why the Ball method may give results and figures which indicate that labor should be possible when actually it is not.

In the discussion of this paper, Dr. P. E. Wigby states that more important information than the actual measurements is obtained from the roentgen examination in cases of suspected contraction or certain short diameters. He believes that significant asymmetry will be apparent to the experienced observer and that actual mensuration may not be necessary.

One drawing; 1 table.

S. F. THOMAS, M.D.
Palo Alto, Calif.

Influences of Posture on the Urinary Tract in Pregnancy. John Parks and Michael A. Puzak. Am. J. Obst. & Gynec. **55:** 636–643, April 1948.

This article will have to be read in the original to be fully appreciated. The authors made serial pyeloureterograms of pregnant women in various positions, and interpreted these pyelo-ureterograms as indicating that posture influences the urinary tract in pregnancy in the following manner:

1. There is no remarkable change in the position of the kidneys or in the contour of the abdominal ureters with changes in posture.

2. The pelvic portions of the ureters which pass

through the base of the broad ligaments are carried upward and downward with changes in position of the gravid uterus.

3. In an upright position and with good abdominal support, many uteri rotate to the right. This occurs irrespective of the position of the fetus. When the uterus rotates, the transligamentous portion of the ureter is carried along with the large uterine vessels and Mackenrodt's ligaments. Whether or not great stretch, torsion, and reduction in the lumen of the right ureter result from the dorsal and downward displacement brought about by dextrorotation has not been demonstrated. This is a possible explanation for the greater degree of dilatation usually present in the right ureter.

4. Contrast medium in the kidney pelves and ureters becomes diluted and is eliminated more rapidly when the weight of the uterus is displaced upward by 15-degree elevation of the foot of the bed than with the patient in an upright position.

5. A generous fluid intake plus rest in bed for twenty to forty-five minutes once or twice daily, preferably with the hips higher than the shoulders, will avoid prolonged urinary stasis and help prevent infection.

6. Pregnant patients with costovertebral pain due to spasm and dilatation of partially obstructed ureters receive relief from elevation of the foot of the bed. The exact mechanism which produces this relief is not known, but the theory is advanced that upward displacement of the gravid uterus releases tension and torsion of the pelvic portion of the ureter, thereby removing spasm and obstruction to urinary flow.

Six roentgenograms; 1 drawing.

HUGH O'NEILL, M.D.
Cleveland, Ohio

Facts and Fantasy in the Study of Female Infertility. John Stallworthy. J. Obst. & Gynaec. Brit. Emp. **55:** 171–180, April 1948.

This is a rather general discussion of the various causes for female infertility; only the part dealing with insufflation and hysterosalpingography will be abstracted here.

Since the development of Rubin's test for determining the patency of the fallopian tubes, much attention has been focused on this method of investigation and it has been credited with therapeutic as well as diagnostic value. In the author's series of 1,000 cases seen in a fertility clinic, the incidence of apparent blockage, *i.e.*, no evidence of tubal patency either on repeated insufflation tests or on repeated use of insufflation and lipiodol injection, was 21.6 per cent. The use of spasmolytics, however, such as nitroglycerine, prior to examination reduced this figure to 12.8 per cent. An analysis of the last 171 patients in the series gave a similar incidence of apparent blockage, 21 per cent, and a corrected figure of 9 per cent. The author believes that the actual incidence is even lower and that his figures include patients with apparent occlusion due to uterotubal irritability unrelieved even by nitroglycerine. In series reported by others the incidence has been given as 26 to 50 per cent.

On the basis of the above figures, it is claimed that unless effective steps are taken to relieve hitherto unsuspected uterotubal irritability, the results of the infertility tests and lipiodol investigation are likely to have a 100 per cent error.

A detailed study of 111 patients in whom the uterus and fallopian tubes were investigated under the fluoroscope indicated that probably the most common cause of unilateral uterotubal blockage is the lack of synchronization of waves of contraction originating at the uterine cornua.

Nine roentgenograms; 3 kymographs.

THE GENITO-URINARY SYSTEM

The Renal Manifestations of Periarteritis Nodosa. R. K. Womack and W. R. Mathews. J. Urol. **59:** 733–747, April 1948.

The nature and etiology of periarteritis nodosa are briefly discussed, and literature indicative of the frequency of urinary signs and symptoms in this disease is cited. Hematuria is listed as occurring in 48 per cent and hypertension in 58 per cent of reported cases.

Three cases are presented in which the symptoms were suggestive of urinary tract disease. The first patient was a 38-year-old white male who had attacks of pain in the right side radiating to the right testicle and thigh, accompanied by nausea but no vomiting. Although his blood pressure was normal at first, hypertension developed later, with progressive urinary failure culminating in death. Retrograde pyelography showed the right kidney to be somewhat smaller than the left and some hydronephrosis on that side. Autopsy revealed lesions of periarteritis in the brain, chest muscles, liver, renal arteries, and kidneys. The provisional clinical diagnosis was nephrolithiasis.

The second case was that of a 53-year-old woman whose complaints were pain and a lump in the left flank. Excretory urography showed an apparently normal right kidney, but no dye was excreted by the left kidney in forty-five minutes. Retrograde pyelography showed calyectasis, pyelectasis, and ureterectasis. At operation there was massive perirenal hemorrhage, apparently from the renal artery, which had to be clamped almost at the aorta. The clamp came away and the patient died of hemorrhage the twelfth postoperative day. Microscopically the kidney contained several areas which were characteristic of periarteritis nodosa.

The third patient, a colored male aged 21 years, was ill only one month. His illness began with severe headache of two days duration, followed by weakness, abdominal pain accompanied by nausea and vomiting, and bloody urine. His blood pressure was 246/170. He grew progressively worse and died eleven days after admission to the hospital. The pancreas, intestinal tract, prostate, and urinary bladder showed lesions of periarteritis nodosa, but none was found in the kidney. The pathological findings in the latter were those of malignant hypertension and uremia.

The authors point out the pitfalls presented by this type of case re-emphasizing the frequency of urinary tract involvement in periarteritis nodosa.

Three roentgenograms; 5 photomicrographs; 1 photograph.

PAUL R. NOBLE, M.D.
University of Pennsylvania

Renal Complications of Hyperparathyroidism. Edgar Burns and C. Mark Whitehead. J. Urol. **59:** 664–673, April 1948.

The authors present four cases of hyperthyroidism with associated renal calcification or calculi in the urinary tract. Three patients had presenting symptoms of renal involvement and the other complained of symptoms due to decalcification of the skeletal system.

A parathyroid adenoma of benign character was diagnosed in each case and hypercalcemia and hypophosphatemia were routinely present.

Treatment consisted of removal of the primary adenoma and renal complications were dealt with after the approved surgical fashion. Blood chemistry returned to normal levels after the removal of the adenoma in 2 cases, but only after surgery and irradiation in the third. Operation was refused by the fourth patient.

Eight roentgenograms; 2 photomicrographs; 1 table.

HORACE G. BUTLER, M.D.
University of Pennsylvania

Subepithelial Hemorrhage of Renal Pelvis Simulating Neoplasm. William Antopol and Lester Goldman, Urol. & Cutan. Rev. **52:** 189–195, April 1948.

Seven cases of subepithelial hemorrhage of the renal pelvis, simulating a tumor, are reported. In all instances, a filling defect was demonstrable by pyelography consistent with that due to a renal neoplasm. This was due to the subepithelial clot. Renal infarcts were present in 5 cases. In 4 cases, there was a congenital anomaly of the kidney.

The authors are of the opinion that the hemorrhage was due to a vascular injury.

A single x-ray examination is not sufficient to differentiate blood clot from tumor. Repeated pyelograms may reveal absorption of the clot.

Thirteen illustrations (5 roentgenograms); 1 table.

MAURICE D. SACHS, M.D.
Cleveland, Ohio

TECHNIC

Axial Stratigraphy. Alessandro Vallebona. Radiol. sperimentale 2: 95–109, March-April 1948. (In Italian.)

The author describes an extremely interesting technical development which permits cross-sectional laminagraphs of the human body. The apparatus consists of two horizontal platforms which can be made to rotate simultaneously. One platform carries the film, the other the patient. The axes of both platforms are aligned in a vertical plane with the central ray, which is directed at the film so that it reaches it at a high degree of obliquity after passing through the patient. The resulting radiographs are surprisingly clear and illustrative.

This method should find application in many special diagnostic problems. The same number of *Radiologia Sperimentale* carries articles by G. Benedetti, by A. De Maestri, by A. Passeri, and by A. Rollandi, describing the application of axial stratigraphy to the diagnosis of disease of the cervical region, of the chest, and of the esophagus. The abstractor feels that Vallebona and his co-workers have added a valuable tool to roentgen diagnosis.

Four roentgenograms; 4 photographs; 1 drawing.

CESARE GIANTURCO, M.D.
Urbana, Ill.

A Viscous Diodone as a Substitute for Iodised Oil. Maurice W. H. Mackay. Brit. J. Radiol. **21:** 204–205, April 1948.

A solution of 35 per cent diodone in 7 per cent polyvinal alcohol is advocated for uterosalpingography and the exploration of sinus tracts. The substance is non-toxic and not irritating. It is quickly absorbed and excreted by the kidneys. Inadvertent intravenous injection is not injurious. One disadvantage in uterosalpingography is that the medium is absorbed so rapidly that twenty-four hour examinations cannot be made. The technic of injection is the same as with iodized oil.

Two roentgenograms.

SYDNEY J. HAWLEY, M.D.
Seattle, Wash.

RADIOTHERAPY

Verrucous Carcinoma of the Oral Cavity. Lauren V. Ackerman. Surgery **23:** 670–678, April 1948.

In the past seven years the author has noted a variety of squamous carcinoma which he describes as having a typical course with characteristic gross and microscopic findings. This type of lesion is designated as verrucous carcinoma and should be separated from other epidermoid carcinomata because of the excellent prognosis, with proper treatment, despite extensiveness.

Thirty-one such cases have been seen; 26 in men and 5 in women. The majority of the patients were aged, and there seemed to be a definite correlation with tobacco chewing, with poor-fitting dentures, poor oral hygiene, and carious and jagged teeth as other frequent findings.

Eighteen of these lesions were of the buccal mucosa, 8 of the lower gingiva, 1 of the upper gingiva, 2 of the hard palate, 1 of the tongue and 1 of the tonsil. The duration was, in general, considerably greater than one year.

The lesion grows rather slowly to extend over a wide area; it is occasionally painful but seldom bleeding. It invades locally and may present externally by invasion of the cheek, producing a mass beneath the mandible, or it may involve the buccal commissure Those arising from the alveolus invade the underlying soft tissue and quickly become fixed to the mandibular periosteum. Infection is common and causes somewhat confusing regional node enlargement.

Microscopically, the transition between atrophic epithelium and tumor is not sharp. The first change noted is a piling up of keratin on the surface, with beginning downgrowth of fingers of epithelium which push their way into rather than infiltrate the deeper tissues, and finally undergo cystic degeneration. The lymph nodes are usually surrounded rather than infiltrated. In this series, there was only one instance of lymph node involvement and none of distant metastasis.

Local recurrences are common in inadequately treated patients. Radiation is successful with small superficial lesions, but for more extensive ones surgery —sometimes with mandibular resection—is advocated. Radiation following surgery was employed seven times without significant statistical improvement over either method used alone.

Excellent gross and microscopic illustrations accompany the article.

Six photographs; 6 photomicrographs.

JOSEPH D. CALHOUN, M.D.
University of Arkansas

Roentgen Treatment of Cancer of the Esophagus. Jacob R. Freid. Am. J. Roentgenol. **59:** 551-564, April 1948.

In competent hands surgery is the treatment of choice for operable carcinomas of the esophagus. The majority of these growths, however, are inoperable when first seen, and for these, as well as for operable lesions when adequate surgery is not available, roentgen therapy is indicated. The use of interstitial or intracavitary radium carries serious risk of perforation, and except for small flat growths is inadequate for complete destruction of the tumor.

Successful roentgen treatment requires multiple ports (at least six), an adequate daily tumor dose (150 to 200 r), and a total tumor dose of at least 5,000 r administered within thirty to forty days. At Montefiore Hospital (New York) from which this report comes, both 200-kv. and 400-kv. therapy are utilized. The clinical impression is that 400 kv. offers some advantages; the depth dose is greater, skin reactions are less severe, and the radiation is better tolerated.

Perforation is a frequent complication of esophagea carcinoma, and one case is briefly presented in which this appeared to be hastened by irradiation. Recurrence of dysphagia after an initial favorable response may be caused by stricture formation at the site of the lesion. It should not be considered as due to recurrence without proof, since damage to the lungs or mediastinum is much more likely to result from a second course of therapy even though no ill effects followed the first course.

A series of 13 cases treated at Montefiore Hospital is presented as offering evidence of the value of irradiation as a palliative procedure in esophageal carcinoma. Since this hospital is an institution for the care of the chronically ill, most of the cases were well advanced on admission. Life appears to have been prolonged, and, in 3 of 4 cases coming to autopsy some time after treatment, no evidence of carcinoma was found, while the fourth showed only a few degenerating cancer cells. There were no five-year survivals, but the author adds an account of a patient treated in private practice who was alive and well after seven years and seven months.

Nine roentgenograms; 3 photographs; 6 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Rôle of Transvaginal Roentgentherapy in the Treatment of Carcinoma of the Cervix. J. A. del Regato. Surg., Gynec. & Obst. **86:** 480–486, April 1948.

Transvaginal roentgen therapy has acquired a definite position in the treatment of carcinoma of the cervix; judiciously employed, it is a valuable adjunct of external pelvic irradiation and is capable of replacing, with certain advantages, the classic methods of intracavitary radium therapy.

The author's patients received transvaginal therapy immediately following a course of external irradiation which had lasted about six weeks. In general, 10 consecutive treatments of 400 r, or a total of 4,000 r in eleven days, were delivered to the cervix level.

Complications, such as "bloody stools" (15 per cent), lower abdominal gas pains, and moderate bowel obstruction, were seen in a few of the patients. In one patient having involvement of the bladder base a fistula developed. Pollakiuria was relatively frequent but of short duration.

Over-all salvage based upon a three-year study of all stages represented in 76 patients was 44 per cent, but the author cautions against the comparison of this figure with those obtained by corrected five-year studies.

All patients in the series reported were treated intravaginally with 110 kv. at 25 cm. Since this report, patients are being treated with 140 kv. and 0.5 mm. copper filtration.

Six photographs; 2 drawings.

J. P. TOMSULA, M.D.
University of Pennsylvania

Carcinoma of the Cervix in an Urban Population. A. W. Diddle and T. R. Bennett. Am. J. Obst. & Gynec. **55:** 669–674, April 1948.

This report gives a cross-section of experience in treating cervical carcinoma in Dallas, Texas, from Jan. 1, 1936, to Jan. 1, 1946. The study is based on 992 women for whom histologic diagnosis was available. For reasons set forth in the paper, accurate statistical data as to results could not be presented and therefore only trends were determined.

The number of patients in the pre- and post-menopausal period of life was approximately equal. Eighty per cent were white and the remainder Negro or Mexican. The patients ranged in age from nineteen to eighty-seven years; 5 per cent were under thirty and 16.3 per cent over sixty.

The symptoms bringing most of the patients to the doctor were vaginal bleeding and leukorrhea. In 44.6 per cent of the patients symptoms had been present for less than six months; 17.4 per cent had symptoms for six to twelve months; 6.6 per cent for thirteen to twenty-four months; 3.2 per cent for twenty-five to thirty-six months; for 28.2 per cent data were not available.

The histologic diagnosis was epidermoid carcinoma in 932 cases and adenocarcinoma in the remaining 60. The author has used the Schmitz classification for grading the cases clinically. Fifty-seven patients were in Class I, 172 in Class II, 302 in Class III, and 174 in Class IV; 290 were unclassified.

Treatment was divided into two categories, that given before cervical carcinoma was suspected and that administered after cancer was suspected. The technic of administering x-ray and radium varied, but in general a total of 3,500 to 5,000 mg. hr. of radium was delivered to the cervix and parametria. Two to three thousand roentgens measured in air were given to each of two pelvic ports located anteriorly and posteriorly. When hysterectomy was done, external irradiation was usually given postoperatively, rarely preoperatively. Where subtotal hysterectomy was done originally, without suspicion of cancer, an interval of three to twenty-four months elapsed before giving x-ray or radium therapy, or both. Approximately one-tenth of the women were re-irradiated six or more months after the initial period of treatment.

It was apparent that the clinical grade of the tumor was more important than the method of irradiation in determining future prognosis. Simple total and subtotal hysterectomy were performed with about equal

frequency from 1936 to 1948 for missed or proved cases of carcinoma of the cervix. Two-thirds of the total hysterectomies were done deliberately after the diagnosis was established or suspected, while one-third were performed in cases in which a malignant growth was not suspected. Three- and five-year survival rates are summarized in the paper. Their analysis indicates that total hysterectomy followed by irradiation, as contrasted with irradiation alone, did not improve the chance for five- and three-year survival. Actually certain types of sequelae were more common after total hysterectomy than in unoperated cases. The results reported compare favorably with those collected by Miller (Am. J. Obst. & Gynec. **46:** 625, 1943) and Heyman (Acta. obst. & gynec., Supp. II, 1938) from different parts of the world.

Seven tables.

HUGH O'NEILL, M.D.
Cleveland, Ohio

Late Recurrence of Cervical Carcinoma Following Radiation Therapy. Harold Speert. Am. J. Obst. & Gynec. **55:** 533–537, March 1948.

The purpose of this paper is to record two extraordinary cases from the Gynecological Service of Roosevelt Hospital (New York) which show that cervical carcinoma may progress slowly, or perhaps even lie dormant for long periods after treatment by irradiation, during its later clinical stages.

CASE I: A 52-year-old white woman was treated for primary carcinoma of the cervix in April of 1922 at the age of thirty-five years. Her cervix was reported at that time as about 5 cm. in diameter with a hard, nodular surface which was beginning to ulcerate. The uterus was moderately movable, but there seemed to be some "shortening of the right parametrium." The biopsy report was "epithelioma, type uncertain." Treatment consisted of 100 mc. hours of radon administered in each of three positions by vaginal bomb on April 17, 1922, and 3,000 mc. hours administered by platinum cervix tandem on the following day. This was followed by a cycle of low-voltage pelvic x-ray irradiation to two anterior and two posterior fields on April 19 and 20. The patient remained under observation for twelve and one-half years and showed no evidence of residual or recurrent tumor. On Sept. 19, 1939, she was admitted to Roosevelt Hospital complaining of vomiting, diarrhea, and lower abdominal pain of eighteen days duration. The vagina was constricted and filled with hard friable tumor. Biopsy showed only granulation tissue. The patient died Oct. 18, 1939. At autopsy the anatomic diagnosis was "carcinoma, primary in cervix, with extension to the fundus, bladder, rectum, ovaries, and fallopian tubes, and metastatic invasion of the periaortic lymph nodes, liver, and diaphragm." Ureteral obstruction, with hydroureter and hydronephrosis were also present. Sections of this tumor were compared with those of the original cervical biopsy of seventeen and one-half years previously and they could not be distinugished from one another, so completely similar were they in histologic detail.

CASE II: A 33-year-old married Negro woman was seen in April 1925, complaining of dysmenorrhea, intermittent backache, and vaginal discharge for two years. Histologic examination revealed cervical carcinoma of the epidermoid type. On April 16, 1925, 50 mg. of radium was applied in the cervical canal for twenty-four hours; and between April 20 and July 14 the patient received "a filtered x-ray treatment through each of six pelvic portals, with the 200-kv. machine at a target-skin distance of 50 cm.—three exposures for thirty minutes each and three for forty minutes." The patient returned regularly to the Out-Patient Clinic until 1931. She was not seen again until November 1944. She then stated that since 1936 she had experienced a foul, blood-tinged vaginal discharge, although she had not menstruated since her previous radiotherapy. Pelvic examination disclosed a hard, friable mass which involved the cervix and adjacent vaginal walls, with slight fixation of the parametria. Biopsy showed epidermoid carcinoma, grade III. During the next few weeks the patient received twenty deep x-ray therapy treatments through four pelvic portals, a total dose of 6,000 r. She was readmitted in February of 1945 with extension of the tumor. Cystoscopic examination indicated blockage of the right ureter by the growth. Death occurred in May 1945.

Three photomicrographs.

HUGH O'NEILL, M.D.
Cleveland, Ohio

Peyronie's Disease and Its Treatment with Radium. Robert E. Fricke and James H. Varney. J. Urol. **59:** 627–630, April 1948.

The treatment for Peyronie's disease has been extremely varied, and not very successful. The authors are of the opinion that the use of radium offers the best results and describe their method. The features consist of properly extending the penis, so that the whole of the shaft is adequately treated, and placing the radium at a distance, thereby avoiding injury to the normal tissues. Three 50-mg. tubes of radium filtered with 1 mm. platinum, are placed over the shaft on wooden blocks 1 inch thick and are left for twelve hours. This is said to give a suberythema dose. The treatments are spaced three months apart. If no apparent benefit is obtained, no further radium is used after the third application.

Over a six-year period a series of 141 cases were treated. Of the 112 cases traced, excellent results were obtained in 37.5 per cent. Definite benefit was obtained in over 50 per cent of cases. The average number of treatments per patient was 1.5. The youngest patient treated was twenty-seven. The average age was fifty-three years. The age of the patient, duration of symptoms before treatment, and the number of treatments given did not seem to be factors definitely influencing the result.

One table.

DAVID S. MALEN, M.D.
University of Pennsylvania

Testis Tumors: Report on 250 Cases. Lloyd C. Lewis. J. Urol. **59:** 763–772, April 1948.

A general survey of tumors of the testis is given, with particular emphasis on a pathological classification and a recommendation for orchiectomy as the preferable treatment for any type of testicular tumor. The classification offered by the author is based not only on the pathological structure but also on the embryological form, radiosensitivity studies, and results of combined surgical and radiation treatment. Three main groups

are recognized: (1) tumors of the supporting tissues, (2) tumors of interstitial cells, (3) tumors of germ-cell origin, the last group including seminoma, embryonal carcinoma, teratocarcinoma, and teratoma.

A series of 250 cases is reviewed, with radical orchiectomy in 169. While it is too early to present statistics on the value of radical surgery, the author recommends treatment as follows. For benign interstitial-cell tumors simple orchiectomy is probably sufficient. For teratomata, radical orchiectomy is indicated without radiation therapy. For seminoma, simple orchiectomy plus radiation therapy is probably sufficient; 1000 r to the entire retroperitoneal lymph drainage area is recommended. In these cases, radical operation may aid in planning radiation therapy. For undifferentiated carcinoma, adenocarcinoma, and papillary adenocarcinoma, radical orchiectomy is indicated, followed by prophylactic roentgen therapy not to exceed 3,000 r. For trophoblastic tumors, choriocarcinoma, and chorioepithelioma radical orchiectomy is indicated; radiation therapy in dosage of 5,000 r should not be used except when inoperable metastatic nodes remain. For teratoma with malignant embryonic elements, irradiation is indicated only when inoperable metastatic nodes are present.

Six photomicrographs (in color); 1 table.

ARTHUR W. PRYDE, M.D.
University of Pennsylvania

Roentgen Ray Epilation: An Improved Measuring Device. Meyer L. Niedelman. Urol. & Cutan. Rev. **52:** 231–232, April 1948.

A device which provides for accuracy in epilation in the treatment of tinea capitis is described. This consists of an adapter which can be fitted to any x-ray unit and a movable centering rod set for 20 cm. The scalp (19 to 22 inches) is divided into five treatment areas and treated at one session. No cone is used. If children are restless, the treatment can be given in two sessions. The device has been found time-saving and accurate.

Two photographs.

MAURICE D. SACHS, M.D.
Cleveland, Ohio

RADIOACTIVE ISOTOPES

Measurement of Radioactive Isotopes. Leon F. Curtiss. National Bureau of Standards Circular 473, 1948.

The determination of the number of radioactive atoms in a sample of a radioactive isotope has beome a matter of importance as these isotopes have not only become an article of commerce but are also used in biological and medical experiments and in the treatment of disease. Uniform quantitative results in all laboratories can be obtained only by using procedures that will yield absolute measurements or by the use of uniform standards of comparison that will, under proper conditions of measurement, give the same result whenever the determination is made.

This 12-page pamphlet, intended to accompany radioactive standards and calibrated samples of radioactive isotopes, contains a discussion of the principles of measurement of radioisotopes in absolute terms, with explanation of units and illustrative examples of precautions that must be taken in measurements to determine disintegration rates. A simple chart for computation of radioactive decay is included.

Two charts; 1 table.

The pamphlet is available from the Superintendent of Documents, Washington, D. C.

Effects of Radioactive Sodium on Leukemia and Allied Diseases. Preliminary Report. T. C. Evans, M. Lenz, C. P. Donlan, and M. J. LeMay. Am. J. Roentgenol. **59:** 469–481, April 1948.

Radioactive sodium has not been used extensively in the therapy of generalized neoplastic disease, primarily because it does not tend to be concentrated in rapidly growing tissue, as does radioactive phosphorus. Nevertheless, it does possess certain advantages. Its half-life is only 14.8 hours, so that the irradiation is practically all given off in one to two days. This makes much easier the regulation of dosage and observation of results. The shortness of the half-life, however, limits the use of the isotope to areas within a few hours drive of a cyclotron.

Radiosodium therapy would seem to have certain advantages over the usual type of roentgen therapy in that it includes the entire body, is protracted over a two-day period, and the radiation is relatively more intense in the blood and other body fluids. Because of the penetrating beta and gamma radiation emitted, heavy lead shielding is necessary for the protection of those working with the isotope.

The authors have treated 24 cases, 19 of which are presented here. The radiosodium was given by mouth as a dilute solution of sodium chloride. No rigid plan of treatment was adhered to other than an attempt to reduce symptoms with a series of treatments and to give an occasional dose thereafter as indicated. The first treatment, which was considered as a test dose, was usually less than 180 microcuries per kilogram of body weight.

Subjective and objective improvement was noted in chronic forms of leukemia and polycythemia vera. Patients who had become resistant to roentgen therapy were benefited for only a short time. Very acute cases showed no improvement at all. Terminal cases of Hodgkin's disease, lymphosarcoma, and leukemia received some relief of pain but the progress of the disease was not stopped.

Administration of radioactive sodium is held to afford a simple and effective means of giving total body irradiation when this is indicated. Like radioactive phosphorus, it does not cause radiation sickness.

Nine graphs; 2 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

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